



# Oral Hairy Leukoplakia in Immunocompetent Patients Revisited with Literature Review

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## Abstract

Oral hairy leukoplakia (OHL) is an Epstein-Barr virus (EBV) related lesion seen in severely immunocompromised patients especially, those with concomitant human immunodeficiency virus (HIV) infection. It has been rarely reported in immunocompetent patients. OHL most often presents on the lateral border of the tongue as an asymptomatic, white, and corrugated plaque that does not rub off. With Institutional Review Board (IRB) approval, the University of Florida Oral & Maxillofacial Pathology Biopsy Service archives spanning 1994–2020 were queried. All cases of OHL affecting immunocompetent patients were identified. Data related to age, gender, clinical presentation, results of Epstein-Barr virus in situ hybridization (EBER-ISH), and periodic acid–Schiff (PAS)-fungus stains were recorded. Medical history and histology of all cases were reviewed for confirmation of diagnosis. A total of 11 cases were identified, the majority of which were males (63.6%) with a mean age of 62 years. All patients were Caucasian. Lesions entirely were located on the lateral borders of the tongue. OHL should not be considered pathognomonic for HIV infection and should be included in the differential diagnoses of keratotic lesions affecting the lateral border of tongue even in immunocompetent elderly patients. The etiology of OHL in this group of patients is not clearly understood.

**Keywords** Oral hairy leukoplakia · Epstein-Barr virus · HIV-negative patients · Immunocompetent

## Introduction

Oral hairy leukoplakia (OHL) is an Epstein-Barr virus (EBV) related lesion. EBV, also known as human herpesvirus 4 (HHV4), is a double-stranded DNA virus belonging to the Herpes virus family. It is one of the most common human viruses and is estimated to infect more than 90% of the world's adult population. It is mainly transmitted via saliva [1]. After the primary infection, EBV remains latent in circulating memory B lymphocytes and oral keratinocytes. Hence, EBV is almost always present in the oral fluids. EBV reactivation occurs either within the B lymphocytes or from cells in the oral epithelium [2–5]. In addition to OHL, EBV has been implicated in other conditions such as infectious mononucleosis and Burkitt's lymphoma [1, 6].

Since the initial description of OHL among homosexual men with human immunodeficiency virus (HIV) in 1984 by Greenspan, this lesion was considered pathognomonic for HIV infection and acquired immune deficiency syndrome (AIDS). It affects more than 50% of HIV/AIDS patients [7, 8]. OHL has been reported in HIV-negative-immunocompromised patients such as transplant recipients [9, 10]. Moreover, OHL has been rarely reported as an adverse effect of localized immunosuppressive medications such as topical or inhaled steroids [2]. Recently, rare cases of OHL in immunocompetent patients have been reported, especially in elderly patients, and as a result, clinicians must be aware that OHL is no longer exclusive to HIV patients.

OHL classically presents as an asymptomatic, white patch with a shaggy or corrugated surface that does not rub off. Typically, the lateral border of the tongue, either unilaterally or bilaterally are commonly involved. However, in rare instances, the buccal mucosa, soft palate, pharynx, or esophagus, may be involved. Importantly, OHL has unique histologic characteristics [2, 11].

The etiopathogenesis of OHL is not fully understood, and the mechanism of latent EBV reactivation by the circulating

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infected B lymphocytes, oral epithelial cells, or contacting EBV infected bodily fluids remains controversial [2–5].

This study underscores the rarity of OHL in immunocompetent patients. Therefore, it is prudent to consider OHL in the differential diagnoses for white lesions affecting the lateral tongue in elderly patients irrespective of HIV or immune status.

## Patients and Methods

For this study, the archives of the University of Florida Oral and Maxillofacial Pathology Biopsy Service was queried between 1994 and 2020. Eleven cases of OHL in otherwise healthy immunocompetent patients were identified. The following parameters were analyzed: patient age, gender, medical history, clinical presentation, EBV in situ hybridization (EBER-ISH) results, and presence or absence of candida verified by Periodic Acid Schiff (PAS) staining. Exclusion criteria included cases with incomplete data or with known immunosuppressive conditions such as HIV, organ transplantation, or malignancies. Histologic samples from all the cases were reviewed to ensure the accuracy of the diagnosis.

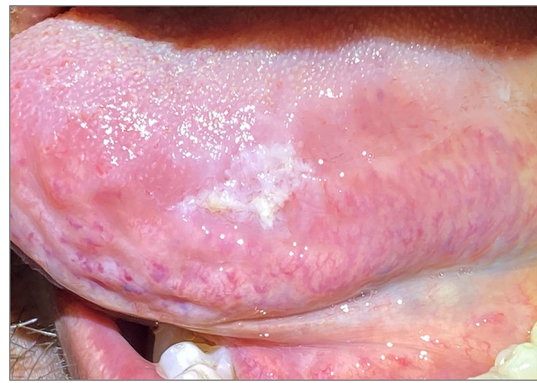
## Results

A total of eleven cases of OHL in otherwise healthy immunocompetent patients were identified. Seven (63.6%) of the patients were males, yielding close to a 2:1 male to female ratio. The mean age was 57.3 years for males, 70.3 years for females, and 62 years for both groups combined. All patients were Caucasian. Only one patient was a known smoker.

The most common clinical differential diagnosis was hyperkeratosis ( $n=7/11$ , 63.6%), while dysplasia and squamous cell carcinoma were considered in the remainder of the cases ( $n=4/11$ , 36.4%).

The clinical presentation most frequently included asymptomatic, white, leukoplakic, non-ulcerated, patch, or plaque that could not be rubbed off. (Fig. 1). All lesions were unilateral and located on the lateral borders of the tongue. There was no difference in the frequency of lesions between the left or right lateral border of the tongue. The time elapsed from the onset of the lesion to the histopathological diagnosis ranged between a few months to years.

All cases shared a common histomorphology including a thickened corrugated, and/or shaggy parakeratin layer with acanthosis. The spinous cells especially toward the surface exhibited a ring or band-like zone of nuclear chromatin material surrounded by abundant lightly stained cytoplasm (Fig. 2a). Within the superficial epithelial cells, distinct nuclear clearing (nuclear beading) with a stippled chromatin pattern was noted in all cases (Fig. 2b). Dysplasia or atypia



**Fig. 1** Thick and shaggy white lesion on the left lateral border of the tongue

was not noted in any of the cases. All cases were stained with PAS for fungus and only two cases exhibited superficial candidal colonization. In situ hybridization for Epstein Barr encoded RNA (EBER-ISH) was performed and was positive in all cases with adequate controls (Fig. 3).

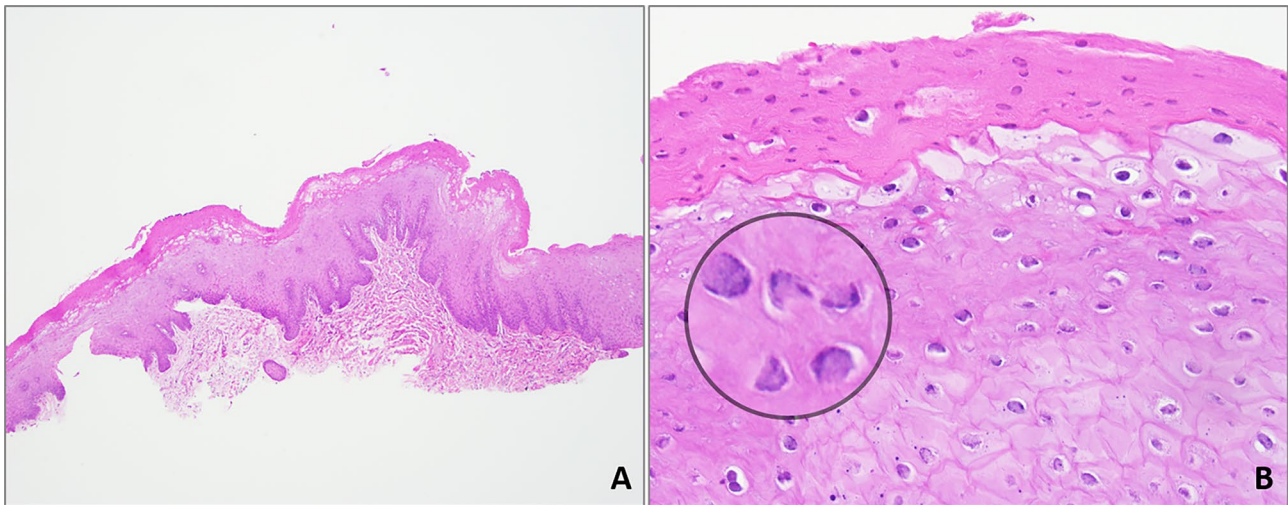
## Discussion

This study describes the demographics, clinical presentation, and histopathological features of 11 cases of OHL. Our results are in agreement with other reports with respect to male gender predilection and an age range of fourth to seventh decades [2, 11–16].

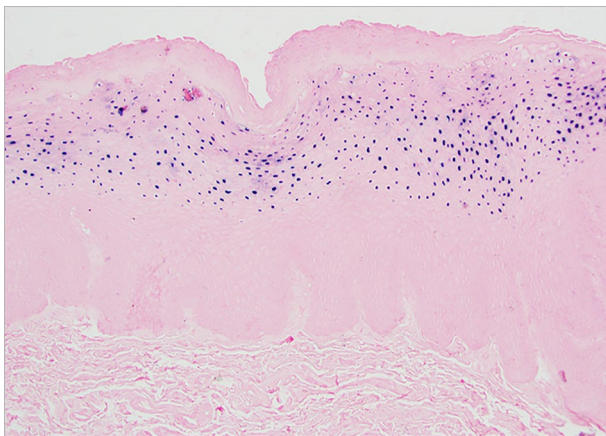
OHL in otherwise healthy patients, as in our cases, is considered very rare [2, 11, 17, 18]. A search of the English language literature including the present cases identified 27 cases of OHL affecting healthy immunocompetent elderly patients (Table 1). All cases associated with immunosuppressive conditions or medications were excluded. The median age noted was 55 years (range, 20–79 years), with male predominance (75%) (Table 1).

Based on the literature and this study, clinically, OHL presents mostly as an asymptomatic, white patch or plaque with a shaggy or corrugated surface that does not rub off. The lateral border of the tongue is the most commonly affected site (79%), either unilaterally (96.3%) as in the present study, or bilaterally (3.7%). The ventral surface is the second most common site of involvement [19]. The presence of a low number of antigen-presenting Langerhans cells on the lateral border of the tongue may contribute to the prevalence of OHL at that site [20]. However, rare cases of OHL affecting other oral mucosal sites such as the buccal mucosa, soft palate, pharynx, or esophagus, have been documented [2, 19].

The exact etiology of OHL in elderly immunocompetent patients remains unclear. However, it has been hypothesized



**Fig. 2** **a** Hyperkeratosis, acanthosis, with prominent intracellular edema are noted at low power, magnification X 20 (H&E\*). **b** Peripheral “beading” of the chromatin is noted in superficial keratinocytes, magnification X 400 (H&E\*). \*Hematoxylin–eosin staining



**Fig. 3** Positive in situ hybridization for Epstein-Barr virus, magnification  $\times 40$

that immunosenescence may play a role in the development of OHL in such patients. Immunosenescence is defined as the state of dysregulation of the immune system as a result of age advancement that may contribute to the increased susceptibility to infection [2, 21]. Immunosenescence might also allow EBV reactivation that is followed by a cascade of events leading to elevation of EBV DNA in the circulating blood [22].

Histopathologically, OHL exhibits a thickened parakeratin layer with surface corrugations. The epithelium is acanthotic and exhibits prominent intracellular edema. This may create confusion for the unaware eye rendering a diagnosis of hyperkeratosis, secondary to trauma. Therefore, in this context, OHL may be misdiagnosed and instead interpreted as a reactive lesion. The characteristic feature of nuclear beading is seen in

the superficial epithelial cells. This is caused by extensive EBV replication that displaces the chromatin to the nuclear margin [12, 19]. Superficial candidal colonization of the parakeratin layer may or may not be present, unlike with OHL associated with immunosuppression. However, this is not a diagnostic criterion. Interestingly, the normal inflammatory reaction to the fungus commonly seen in the underlying lamina propria is usually absent [11, 19]. Identification of EBV using EBER-ISH is required for confirmation of the diagnosis. EBER-ISH is considered the gold standard for identification of EBV in formalin-fixed paraffin-embedded tissue samples [23, 24].

The viral cytopathic effects of Herpes Simplex virus (HSV) include the presence of ‘Tzanck’ cells exhibiting ballooning degeneration usually, within an ulcer [25]. Cytomegalovirus (CMV) commonly presents with the classic “Owl’s eyes” morphology within the affected cells. These are both significantly different from the viral effects of EBV [25].

Diagnosis of OHL in otherwise healthy patients mandates further evaluation of the patient including, extensive review of patient’s medical history, medications, and social history to rule out potential immunosuppressive conditions. OHL is usually asymptomatic, with no risk of malignant transformation, and treatment usually is not needed [17, 19]. Systemic anti-viral therapy might be necessary for symptomatic cases or where esthetics is a concern. A rapid resolution is anticipated; however, recurrence is usually seen with discontinuation of therapy [11, 19].

**Table 1** Cases of oral hairy leukoplakia in immunocompetent patients reported in the literature

No	Reference	Gender	Age	Race if known	Location
1	Eisenberg et al. 1992 [12]	M	48	White	Right lateral tongue
2	Eisenberg et al. 1992 [12]	M	20	White	Right lateral tongue
3	Felix et al. 1992 [13]	M	79	n/p	bilateral tongue and ventral surfaces
4	Lozada-Nur et al. 1994 [14]	M	43	White	Posterior lateral tongue
5	Lozada-Nur et al. 1994 [14]	M	47	n/p	Right lateral tongue
6	Walling et al. 1995 [15]	n/p	48	n/p	n/p
7	Walling et al. 1995 [15]	n/p	20	n/p	n/p
8	Walling et al. 1995 [15]	n/p	79	n/p	n/p
9	Piperi et al. 2010 [2]	F	70	n/p	Right lateral tongue
10	Darling et al. 2018 [16]	M	n/p	n/p	Left ventral tongue
11	Darling et al. 2018 [16]	M	n/p	n/p	Right lateral/ventral tongue
12	Darling et al. 2018 [16]	M	n/p	n/p	Right lateral tongue
13	Darling et al. 2018 [16]	M	n/p	n/p	Right lateral/ventral tongue
14	Darling et al. 2018 [16]	M	n/p	n/p	Left lateral tongue
15	Shanahan et al. 2018 [11]	F	41	n/p	Right lateral tongue
16	Shanahan et al. 2018 [11]	M	30	n/p	Right lateral tongue
17	Present study	M	47	White	Right lateral tongue
18	Present study	M	65	White	Right lateral tongue
19	Present study	M	48	White	Left lateral tongue
20	Present study	F	76	White	Right lateral tongue
21	Present study	M	79	White	Right lateral tongue
22	Present study	F	66	White	Left lateral tongue
23	Present study	F	70	White	left lateral tongue
24	Present study	M	59	White	Right lateral tongue
25	Present study	M	43	White	Left lateral tongue
26	Present study	F	69	White	Right lateral tongue
27	Present study	M	60	White	Left lateral tongue
Results	Female = 6 Male = 18 Not provided = 3		Mean age = 55 years	White = 14 Not provided = 13	Lateral tongue = 19 Lateral/ventral = 3 Ventral tongue = 1 Posterior tongue = 1 Not provided = 3 Bilateral = 1

n/p not provided

## Conclusion

OHL should be included in the differential diagnoses of keratotic plaque-like lesions on the lateral border of the tongue even in otherwise healthy immunocompetent elderly patients. Clinicians should be sentient of the fact that OHL can affect non-HIV patients and that age-related immunosenescence might play a role in the development of OHL in these patients. Raising the awareness of these cases of OHL may lead to increased identification of OHL in immunocompetent patients thereby facilitating further understanding of this entity.

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## Compliance with Ethical Standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical Approval** This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of the University of Florida approved this study.

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