Oral Hairy Leukoplakia in pemphigus Patients: A Case Series

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ABSTRACT:

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Oral hairy leukoplakia (OHL) is an Epstein-Barr virus (EBV)-associated lesion of the oral mucosa and most commonly seen in human immunodeficiency virus (HIV)-positive patients. However, OHL has also been reported in HIV-negative immunosuppressed patients. We present two cases of OHL in pemphigus patients. One lesion was located on the lateral borders of tongue and the other was located on the dorsal of tongue. The diagnosis was confirmed by clinical, polymerase chain reaction for EBV from lesion scraping and excluded oral candidiasis. Smoking, advanced aged and oral pemphigus may be the contributing factors to develop OHL in these patients. Oral acyclovir and gentian violet are effective treatments for OHL in our patients.

Key words: Oral hairy leukoplakia, Epstein-Barr virus, pemphigus

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Introduction

Oral hairy leukoplakia (OHL) is a viral infection of the oral mucosa, caused by Epstein-Barr virus (EBV), also referred to as human herpesvirus 4 (HHV4). It was first described by Greenspan et al. in 1984 in homosexual male patients and was considered a manifestation of human immunodeficiency virus (HIV) infection[1]. Clinically, OHL presents as unilaterally or bilaterally painless white patch with a shaggy or corrugated surface that cannot be wiped off. OHL is most commonly located at lateral margins of the tongue.

OHL has also been reported in HIV-negative immunosuppressed patients including solid organ and bone marrow transplantation, ulcerative colitis, systemic lupuserythematosus, Behcet disease, hematologicalmalignancy, immunosuppressive therapy use, oral pemphigus vulgaris and mucous membrane pemphigoid. Rare cases of OHL in immunocompetent healthy patients have also been documented[2-3].

This case series describes two cases of OHL in pemphigus patients with different medical history.

Case series

Case 1

A 52-year-old male was referred to our dermatology clinic for evaluation of suspected pemphigus vulgaris. He concomitantly complained whitish patches on lateral side of his tongue. The lesion could not be wiped away. He first noticed it about 2 months ago. He denied any pain or discomfort from the area.

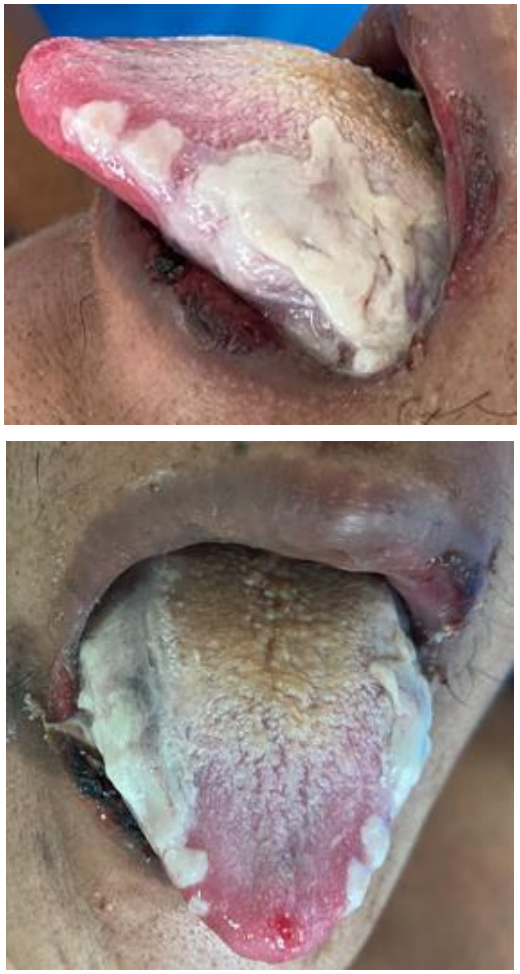

Figure 1 Photos show bilateral white patches on lateral aspect of the patient's oral tongue

On examination, there were bilateral white patches on lateral surface of the tongue with no surrounding inflammation or edema (Figure 1). The remainder of the examination was multiple erythematous eroded patches on soft palate and lips. There was no cervical lymphadenopathy.

The patient's medical history was clear and he did not take any regular medications. He smoked 15 pack-years and consumed 10-20 units of alcohol a week.

He denied the biopsy. However, polymerase chain reaction (PCR) amplification for common *EBNA2* region of EBV was performed from the sample scraped from the right lateral side of the tongue. For EBV genotyping, two separate nested PCR reactions amplifying distinctive regions were also performed according to the protocol previously described[4]. The diagnosis was confirmed by PCR for EBV-1 positive from lesion. The potassium hydroxide (KOH) preparation from the lesion was negative. Result of a serum enzyme-linked immunosorbent assay for HIV was negative. The other blood tests were normal.

The patient was treated with oral acyclovir and application of gentian violet to lesions once a day over a period of 1 month. The total treatment duration of acyclovir was 14 days due to concurrent eczema herpeticum infection. Complete resolution was noted at one-month follow up. There has been no recurrence of OHL in 3 months after treatment.

Case 2

A 71-year-old female with a history of pemphigus vulgaris admitted to our inpatient department due to flare up of disease. She concomitantly presented with diffuse painless white patch lesion on the dorsal of the tongue and could not be wiped off. She was unaware of its duration. Her past medication included prednisolone 20 mg per day but she had not taken it for a month. In addition, her social history was negative for smoking and alcohol drinking.

On oral examination, there was diffuse, soft corrugated white patch on the dorsal of the tongue (Figure 2). The remainder of the examination was multiple erythematous eroded patches on the right buccal mucosa and soft palate.

She denied the biopsy. The diagnosis was made by clinical information, presence of EBV viral capsid antigen (VCA) IgG in blood test and PCR for EBV-1 positive from lesion scraping at the dorsal of the tongue. KOH preparation from the lesion and the past result of a serum enzyme-linked immunosorbent assay for HIV were negative.

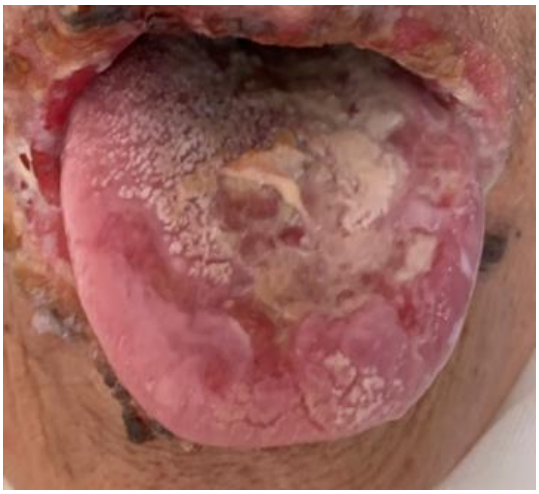

Figure 2 Photo shows diffuse, corrugated white patch on the dorsal of the tongue

The patient was treated with oral acyclovir and application of gentian violet to lesions once a day over a period of 1 month. As in case 1, the total treatment duration of acyclovir was 14 days due to concurrent eczema herpeticum infection. Complete resolution was noted at one-month follow up. There has been no recurrence of OHL in 3 months after treatment.

Discussion

Oral hairy leukoplakia is an EBV-associated lesion of the tongue. Many cases of OHL have been reported in patients who were immunosuppressed other than HIV infection, such as transplant recipients, patients on immunosuppressive medication, hematologic malignancy, oral pemphigus vulgaris and mucous membrane pemphigoid[2-3].

OHL presents clinically as unilaterally or bilaterally asymptomatic white patch with a shaggy or corrugated surface that cannot be scraped off. The most common site of OHL is lateral borders of tongue, but can be found in buccal mucosa, soft palate and floor of mouth[5]. Differential diagnosis includes hyperplastic candidiasis, frictional keratosis, idiopathic leukoplakia, smoking-associated leukoplakia, oral lichen planus or dysplasia lesion.

EBV is a member of the Herpes viridae family and primarily transmitted in saliva. EBV mainly infects B-lymphocyte and epithelial cells. There are two EBV genotypes, EBV-1 and EBV-2, that differ according to DNA sequence and oncogenic potential. EBV-1 is potentially more oncogenic than EBV-2 and plays a role in the pathogenesis of nasopharyngeal carcinoma and lymphoproliferative disorders[6].

Primary EBV infection is usually asymptomatic, and occurs in childhood. But it may cause infectious mononucleosis in adolescence and adulthood. The virus persists lifelong in memory B-lymphocyte following the primary infection. EBV can replicate in B-lymphocyte and oral keratinocyte, thus mature B-lymphocyte and oral keratinocyte serve as reservoirs of latent EBV infection. Reactivation of the latent EBV infection results in productive infection[6].

Three mechanisms have been proposed to explain EBV infection of oral epithelium. First, reactivation of EBV in circulating B-lymphocyte that subsequently infected in Langerhans cell reside in basal layer of oral epithelium. The second mechanism is proposed that virions in oral fluid, shedding from productive EBV replication in epithelium or oral/oropharyngeal lymphoid tissue, can invade differentiated keratinocytes and induce their proliferation resulting in OHL. And the last one, the latent EBV is reactivated as infected cell in basal layer of oral epithelium then spread to the surface of epithelium[6]. The preference of OHL in lateral tongue has been postulated from low numbers of Langerhans cell in this area[7].

Lozada-Nur et al. reported 2 cases OHL in patient with 3-year history of oral pemphigus vulgaris and 5-year history of mucous membrane pemphigoid. Both patients had been treated with potent topical steroid for a long time. Lozada-Nur et al. explained that the appearance of OHL in the patients may be related to the chronic use of potent topical corticosteroid. These preparations may induce transient local immunosuppression through alterations in protective mucosal barrier[3]. The document about risk of OHL in pemphigus lesion alone has not been reported yet.

Apart from topical steroid, many studies have shown OHL in patients with T-cell immunosuppression related to immunosuppressant drugs including systemic corticosteroid, cyclosporine, azathioprine, etc[2].

In addition, Shiboski et al. disclosed a strong positive relationship between smoking and increased incidence of OHL in HIV-positive men. One hypothesis is that components of cigarette smoke affect local cell-mediated immunity by interfering with Langerhans' cells[8].

Piperi et al. have assumed that advanced age may act as a contributing factor in OHL development[9].

The definitive diagnosis of OHL demands demonstration of EBV in the lesional tissue and molecular detection of EBV-encoded RNA by in situ hybridization (EBER) performed on tissue sections is the gold standard[10].

Avoiding invasive procedure (particularly in children), EBV-DNA demonstrated by PCR in oral scrapes is alternative method. A study of PCR of EBV in exfoliated specimens suggested a high sensitivity but low specificity for the diagnosis of OHL. Not only EBV-DNA was demonstrable by PCR in HIV-infected patients with or without clinical OHL but it was also detected in healthy people. However, PCR can be useful for the detection of EBV in oral scrapes, and as an adjunct in the diagnosis of OHL[11]. Nadal D et al.diagnosed OHL in HIV children by PCR detected EBV-DNA from oral scrapes[12].

OHL is a benign disease that does not always require intervention. Indications for treatment include pain, dysphagia or cosmetic concern[13]. A variety of treatment options exist. Topical therapy is the most highly recommended treatment due to the easy use, low cost and fewer side effects. Several studies show that the result of the application of 25% alcoholic solution of podophyllin or 25% podophyllin resin is significant. They described a burning sensation, pain and slight change of taste with a short duration after applying topical podophyllin. Sanchez et al. observed a recurrence rate of 33.3% of OHL treated with 25% podophyllin[14].

Ficarra et al.'s study was performed using acyclovir cream for topical treatment in 23 HIV-positive patients. They found a complete resolution of OHL only in two patients and

showed no recurrence of the lesion 6 months after topical acyclovir cream treatment[14].

A clinical trial study proposed a combined topical therapy of 25% podophyllin and 5% acyclovir cream and compared the results with 25% podophyllin. All lesions treated with podophyllin and acyclovir showed total clinical regression and no recurrence rate was observed[14].

Bhandarker et al performed a study using 2% gentian violet as a topical treatment for OHL in one HIV-positive patient. Gentian violet was applied topically to the lesion for 3 times in one-month period. Complete regression was observed at one-month follow up and there was no recurrence in one year after treatment[14].

Systemic antiviral drugs such as acyclovir, valacyclovir, desciclovirandganciclovirhavebeen usedfor OHL treatment with recurrence observed after discontinuation[14].

In previous report, OHL in oral pemphigus vulgaris improved without treatment after topical steroids were discontinued[3].

In conclusion, we present OHL in 2 pemphigus vulgaris patients without topical or systemic immunosuppressive therapy use. Smoking and senility may be the contributing factors to develop OHL in our patients. Additionally we assume that raw surface from oral pemphigus itself is also possible risk factor to develop OHL. Our patients respond to oral acyclovir with gentian violet application. However OHL can be resolved spontaneously without any treatment.Physicians should always include OHL in differential diagnosis lists when white patches lesions are observed on both lateral and dorsal sides of the tongue in pemphigus patients.

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