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Review article

Oral hairy leukoplakia: The role of Epstein–Barr virus, the occurrence in immunocompetent patients, and the malignant transformation potential

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Abstract Oral hairy leukoplakia (OHL) was first reported by Greenspan et al., in 1984 and it was observed in a group of male homosexuals in the San Francisco. These lesions are predominantly found on the lateral borders of the tongue and show a corrugated or "hairy" surface. The Epstein–Barr virus (EBV) was then detected in these OHL lesions and proved to be involved in the development of the OHL. Besides, the OHL is also seen in people with immunosuppressive states. In this study, we focused on three different aspects of the OHL: (1) the necessity of presence of the EBV in the OHL lesions; (2) the OHL lesions in immunocompetent patients; (3) the potential of malignant transformation in the OHL lesions. In addition to clinical presentations, histopathological examination of the biopsy specimens with the confirmation of the presence of the EBV in the lesions can make the diagnosis more reliable. Moreover, when the OHL occurs in those who are relatively healthy, a thorough survey to find out the possibly insidious diseases or contributing factors is essential. Furthermore, although the evidence to prove the potential of malignant transformation in the OHL lesions is limited, it still need further investigations.

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Introduction

Oral hairy leukoplakia (OHL) was first reported by Greenspan et al., in 1984.[1] They found that there are unusual oral white lesions noted in 37 male homosexuals in the San Francisco area from 1981 to 1984. These lesions are predominantly found on the lateral borders of the tongue and show a corrugated or "hairy" surface. The OHL lesions cannot be rubbed off and usually symptomless.[1]

At the beginning, these newly-described lesions were initially suspected to be associated with the candidal infection and the papillomavirus or herpesviruses. *Candida* is identified in some of these lesions, but only few cases regress after antifungal therapy. Twenty-three (77 %) of thirty cases show positive nuclear staining for papillomavirus in the upper epithelial layer of the lesions. However, herpes-type viruses, rather than papillomavirus particles, can be detected under an electron microscope.[1] The unexpectedly detected herpes-type virus is later proved to be Epstein–Barr virus (EBV) by immunohistochemistry for viral capsid antigen (VCA) and by Southern blot hybridization for EBV DNA.[2]

After the discovery of the EBV in the OHL lesions, it was postulated that the basal epithelial cells of the lateral borders of the tongue may normally harbor the latent EBV in the majority of the adult population who are the EBV-seropositive carriers of that virus. In addition, comparing to the non-lesional oral mucosa from the same patients, there is absence or greatly decreased number of Langerhans cells (LC) in the lesional epithelium, suggestive of the local oral mucosal immune defect in these patients and this may contribute to the pathogenesis of the OHL lesions.[3,4] Succeeding studies have shown the diverse results about these postulations.

The role of EBV in the oral hairy leukoplakia lesions

The first issue is that whether EBV is essential for the diagnosis of the OHL. John S. Greenspan and Deborah Greenspan had tried to establish their diagnostic criteria for the OHL. They considered that both clinical presentations and histopathological features are not pathognomonic, so the test for EBV should be carried out for the suspicious OHL lesions.[3]

However, there were still the EBV-negative OHL lesions reported. Green et al. have reported 16 patients with oral lesions mimicking the OHL but are negative for the EBV tests. These patients with the age between 18 and 68 years are seronegative for human immunodeficiency virus (HIV) with two of them being renal transplant recipients.[5] Epstein et al.[6] also reported cases suggestive of the OHL without the detection of the EBV in the OHL lesions but the individual patient information is not mentioned in the article. Thereafter, sporadic cases have been reported and the clinical information is reviewed and displayed in Table 1.[7–10]

Most authors were uncertain about the nature of these "OHL-like" lesions, even though they tried to interpret as underdetection of the virus, or misdiagnosis.[5,7] Except one

Table 1 Clinical cases of oral hairy leukoplakia (OHL) without the detection of the Epstein–Barr virus (EBV) in the OHL lesions.

Type of study	Year	Author	Patient age	Patient sex	Immune status	EBV	Treatment and outcome
Case report	1992	Fisher et al.[10]	30	F	Unremarkable	ISH (−)	No response to the oral acyclovir
Case report	1993	Itin et al.[8]	21	M	Unremarkable	IHC (−) PCR (−) EM (−)	Spontaneous regression of the lesion
Case report	1993	Itin et al.[8]	28	M	Unremarkable	IHC (−) PCR (−) EM (−)	Persistency of the lesion after 1-year follow-up
Case report	1994	Euvrard et al.[7]	51	F	Receiving renal allograft and treated with cyclosporine, prednisone, and azathioprine	IHC (−) ISH (−)	Regression of the lesion after treatment with either topical retinoic acid or amoxicillin
Case report	2018	dos Reis et al.[9]	29	M	Unremarkable	ISH (−)	Spontaneous regression of the lesion

Abbreviations: ISH = In situ hybridization; IHC = Immunohistochemistry; PCR = Polymerase chain reaction; EM = Electron microscopy.

case reported in the past decade, most of the OHL cases without the detection of the EBV in the OHL lesions were published in the early 1990s (Table 1).[7–10] Thus, in our opinion, this might be explained by the inability to detect the subtle viral load and the lack of advanced techniques to detect the virus in the early 1990s.

The etiological factors of oral hairy leukoplakia

Thus, to date, there have been a consensus that the OHL is EBV-associated, and that the tentative diagnosis can be made by the clinical features and the specific medical history which indicates immune dysfunction, such as HIV infection and receiving organ transplantations or systemic steroid therapy. Histopathological examination and laboratory tests for detecting the EBV can further confirm the diagnosis.[11–13] Despite minority, the OHL lesions could notwithstanding be found in the immunocompetent patients.[14–23] We reviewed the cases that were free of above conditions (HIV infection and receiving organ transplantations or systemic steroid therapy) and listed them in Table 2. To get insight into this phenomenon, we needed to clarify how the EBV involved in the development of the OHL lesions, so we now moved on to the issues about the source of the EBV and its possible pathogenesis for the OHL.

B-lymphocytes are known to be the major target and the reservoir for the EBV.[24–26] The oropharyngeal epithelial cell has also been proved to be another target cell type for the EBV. However, the EBV has been demonstrated to be absent from normal lingual epithelium in the immunocompetent hosts that are previously infected with the EBV.[27,28] Thus, it seemed like that the tongue epithelium was not a good natural reservoir for the EBV. In vitro co-cultivation of the EBV-infected B lymphocytes with uninfected monocytes showed that the EBV can be transmitted to the monocytes. The EBV-infected $CD14^+$ submucosal monocytes can migrate into the epithelium in ex vivo oral epithelium explants, then initiating productive events in the spinous cell layer with the nearby EBV-positive $CD68^+$ and $CD1a^+$ cells. In addition, the EBV-positive monocytes are detected in the peripheral blood of the most HIV-infected individuals. These finding may somehow explain the source of the EBV in the OHL lesions and the possible route of the EBV to enter into the oral epithelium.[29]

The CD21 were the EBV receptors on the B lymphocytes.[24,25] Membranous staining of the CD21 is observed in the spinous cell layers of the parakeratinized stratified squamous epithelium and the presence of the EBV DNA in these cell phenotypes are proved by in situ hybridization (ISH).[30] However, the receptors involved in the epithelial EBV infection may be far more complex and delicate than those in the B lymphocytes. An in vitro study showed that the majority of the EBV-infected epithelial cell lines have negative or extremely low CD21 expression, suggesting of a possible unidentified epithelium-specific binding receptor distinct from the CD21 to mediate the EBV infection.[31] Recently, loss of *BDLF2* (encoding a type II glycosylated envelope protein of EBV, BDLF2) has been related to the decrease of infected cells in organotypic cultures compared to the wild-type, suggesting that the BDLF2 may be essential for intercellular spread of viral infection in the stratified squamous epithelium.[32,33]

There are two alternative phases in the EBV life cycle: lytic and latent.[12] As an orally transmitted virus, the EBV has been proved to be transmitted through the oropharyngeal mucosa without causing prominently productive infection. When the EBV is transported from the apical to the basolateral membranes of the oral epithelial cells, the virions are surrounded by apical surface protrusions and present in subapical vesicles, initiating micropinocytosis and then transcytosis across oral mucosal epithelium rapidly. This process may contribute to delivery of the EBV to the subepithelial B lymphocytes, resulting in a primary EBV infection.[34] After a primary infection, the step to switch the EBV cycle from latent to lytic phases may play an important role in the development of the OHL lesions. This process has been proved to be related to several conditions, such as poor control of cellular immunity over the latent virus, which may be associated with anxiety or stress.[35,36]

At the molecular level, a set of associated genes have been analyzed and displayed; different classes, including the immediate-early, early, and late genes are expressed in order during the EBV lytic replication.[37] *BZLF1* as one of an immediate-early genes of the EBV, its product can bind to the oriLyt (the lytic origin of replication) acting as a transcription activator to turn on the expression of downstream genes to disrupt the EBV latency.[38–40] Recently, epigenetic signals have been found to be involved in its regulation that the increased affinity for the BZLF1 binding to the ZREs (binding sites for BZLF1) with methylation of CpG-containing motifs from a viral lytic promoter allowed to activate other transcription factors, subsequently triggering the EBV lytic replication.[41,42] The BRLF1 is another immediate-early gene product of the EBV, cooperating with the BZLF1 to regulate the viral lytic replications.[43]

The *BMRF1*, as one of early genes of the EBV lytic replication, its product is a DNA polymerase processivity factor, synergetic with the BZLF1 for activation of downstream components of the EBV oriLyt. It can also inhibit the host DNA damage signaling pathway to facilitate the survival of the damaged cells; thus enable the EBV to replicate and persist in human cells.[39,44,45] The BMRF-2 is a glycoprotein binding to integrins, helping the attachment to polarized oral epithelial cells, which is critical for the EBV infection in the oral epithelial cells.[46] The BGLF4, as a viral protein kinase, can modulate some of previously mentioned proteins, such as BZLF1 and BMRF1, to facilitate the optimal oriLyt-dependent viral DNA replication by phosphorylation.[47,48]

The above-mentioned proteins associated with the EBV lytic phase have been proved to be present in the lingual epithelium. The diffuse cytoplasmic BZLF1 expression is found in the basal epithelial cells in the OHL lesions of the HIV positive patients, in contrast, negative in the lingual and gingival epithelium of the HIV-negative individuals. Nuclear localization of the BZLF1, BRLF1, and BMLF1 is found in the spinous cell layer and the above layers with correlation to the distribution of the VCA, indicating that the lytic replication may occur in the upper portion of the epithelium.[49] Similar results of the expression of BZLF1 in the OHL lesions have been demonstrated in another two

Table 2 Clinical cases of oral hairy leukoplakia (OHL) in the immunocompetent patients.

Type of study	Year	Authors	Patient age	Patient sex	Chronic disease	EBV	Oral habit	Treatment and outcome
Case report	1992	Eisenberg et al.[14]	48	M		ISH (+)		Complete regression after biopsy
Case report	1992	Eisenberg et al.[14]	20	M		ISH (+)		Biopsy and no recurrence after biopsy
Case report	1992	Felix et al.[15]	79	M		ISH (+)		
Case report	1994	Lozada-Nur et al.[16]	46	M	*Pemphigus vulgaris*, treated with topical steroids	ISH (+)		Spontaneous regression after discontinuation of topical steroids
Case report	1994	Lozada-Nur et al.[16]	67	F	Mucous membrane pemphigoid, treated with topical steroids	ISH (+)		
Case report	1994	Lozada-Nur et al.[16]	43	M		ISH (+)	Smoking (20 packs per year)	Stable during the follow-up period
Case report	1994	Lozada-Nur et al.[16]	47	M		ISH (+)		Spontaneous regression
Case report	1995	Walling et al.[17]	48			Southern blots (+)		
Case report	1995	Walling et al.[17]	20			Southern blots (+)		
Case report	1995	Walling et al.[17]	79			PCR (+)		
Original article	2010	Piperi et al.[18]	75	M	Chronic obstructive pulmonary disease with inhaled steroids	ISH (+)		
Original article	2010	Piperi et al.[18]	32	M	Chronic obstructive pulmonary disease with inhaled steroids	ISH (+)		
Original article	2010	Piperi et al.[18]	74	F	Chronic obstructive pulmonary disease with inhaled steroids	ISH (+)		
Original article	2010	Piperi et al.[18]	64	F	Chronic obstructive pulmonary disease with inhaled steroids	ISH (+)		
Original article	2010	Piperi et al.[18]	59	M	Chronic obstructive pulmonary disease with inhaled steroids	ISH (+)		
Original article	2010	Piperi et al.[18]	37	F	Chronic obstructive pulmonary disease with inhaled steroids	ISH (+)		
Original article	2010	Piperi et al.[18]	66	M	Chronic obstructive pulmonary disease with inhaled steroids	ISH (+)		
Original article	2010	Piperi et al.[18]	70	F		ISH (+)		

(*continued on next page*)

Table 2 (*continued*)

Type of study	Year	Authors	Patient age	Patient sex	Chronic disease	EBV	Oral habit	Treatment and outcome
Case report	2014	Prasad and Bilodeau[19]	67	M	Chronic obstructive pulmonary disease with inhaled steroids	ISH (+)	Smoking and drinking	Complete regression after 11-month follow-up
Case report	2014	Prasad and Bilodeau[19]	53	F	Asthma with inhaled steroids	ISH (+)		
Case report	2016	O'Brien et al.[20]	56	F		ISH (+)		Antifungal therapy for concomitant candidiasis; regression after 3-month follow-up
Case report	2018	Darling et al.[21]				ISH (+)	Smoking	Spontaneous regression
Case report	2018	Darling et al.[21]				ISH (+)	Ex-smoker	Spontaneous regression
Case report	2018	Darling et al.[21]				ISH (+)	Smoking	Spontaneous regression
Case report	2018	Darling et al.[21]				ISH (+)		Spontaneous regression
Case report	2018	Shanahan et al.[22]	41	F		ISH (+)	Drinking, ex-smoker	
Case report	2018	Shanahan et al.[22]	30	M		ISH (+)	Smoking (2 cigarettes per day for about 10 years) and drinking	
Case report	2018	Shanahan et al.[22]	18	M	Asthma with inhaled steroids	ISH (+)		
Case report	2018	Shanahan et al.[22]	67	M	Asthma with inhaled steroids	ISH (+)	Drinking	
Original article	2021	Alramadhan et al.[23]	47	M		ISH (+)		
Original article	2021	Alramadhan et al.[23]	65	M		ISH (+)		
Original article	2021	Alramadhan et al.[23]	48	M		ISH (+)		
Original article	2021	Alramadhan et al.[23]	76	F		ISH (+)		
Original article	2021	Alramadhan et al.[23]	79	M		ISH (+)		
Original article	2021	Alramadhan et al.[23]	66	F		ISH (+)		
Original article	2021	Alramadhan et al.[23]	70	F		ISH (+)		
Original article	2021	Alramadhan et al.[23]	59	M		ISH (+)		
Original article	2021	Alramadhan et al.[23]	43	M		ISH (+)		
Original article	2021	Alramadhan et al.[23]	69	F		ISH (+)		
Original article	2021	Alramadhan et al.[23]	60	M		ISH (+)		

EBV = Epstein–Barr virus; ISH = In situ hybridization; PCR = Polymerase chain reaction

syudies.[50,51] One of both even confirmed the presence of EBV DNA in mid-to upper-portion of the epithelium and the co-expression of the early antigens (EA), VCA, membrane antigens (MA), and EBV latent proteins (EB nuclear antigen-1, EBNA-1; EBNA-2; latent membrane protein-1, LMP-1) and CD21.[51]

On the other hand, the association of the local immune response with the OHL has also been investigated. Walling et al.[52] found that LC counts are inversely correlated with the EBV replication. The count of LCs regains to the normal level under the inhibited EBV replication by treatment of valacyclovir and it drops down again after discontinuation of valacyclovir. Besides, the process seems to be independently of the HIV infection. Their findings suggested that the EBV possibly evades the oral mucosal immunity by eliminating oral LCs, which facilitates its persistence and results in the development of the OHL.[52] Their conclusion coincided with the disease course of the OHL patients in one previous clinical study, which demonstrated that OHL lesions are completely resolved or significantly reduced during treatment of desciclovir (a prodrug of acyclovir), but some patients develop the OHL lesions again after discontinuation of the therapy.[53]

Taken together, the etiological factors of the OHL are quite sophisticated, involving the local immunity, tissue tropism, transmission pathways, viral replication and of course, the susceptibility of the host. Therefore, the host immunity is important but seems not to be the only determinant of the development of the OHL lesions, which may explain why there are immunocompetent patients with the OHL lesions. In our reviewed cases, there is a relatively high percentage of patients using the topical or inhaled steroids (Table 2), which may somehow suppress the local oral mucosal immunity, leading to the development of the OHL lesions.[16,18,19,22]

The potential of malignant transformation in oral hairy leukoplakia lesions

The association between the EBV and several human malignancies including Burkitt lymphoma, Hodgkin's lymphoma, nasopharyngeal cancers, and gastric cancers has been well recognized.[54—58] Though the EBV could be detected in both lymphoid and epithelial malignancies, the profile of the EBV in the B lymphocytes and epithelial cells are quite different, and the EBV-associated epithelial malignancies seem more complex with many unknowns.[56,59]

As we know, the EBV could switch between the latent and the lytic phase. Due to the relation of the viral lytic replication and the development of the OHL, the genes involved in the lytic replication have been introduced in the previous paragraphs. Regarding to the oncogenesis, the latent genes, such as *EBNA-1*, *EBNA-2*, *EBNA-3*, *LMP-1*, *LMP-2*, and *Epstein—Barr virus—encoded small RNAs (EBER)*, might play a key role whereas the lytic components might contribute to the tumor microenvironment. There is relatively limiting viral gene expression during the latency, so the EBV can reduce the number of viral proteins to prevent from the recognition of infected cells by the cytotoxic T lymphocyte.[12,60] In addition, *LMP-1*, as an oncogene, can facilitate the survival of the B lymphocytes and is able to induce lymphoma in transgenic mice.[61,62]

However, in the OHL lesions, *EBV* DNA, *LMP* mRNA and *EBER* RNAs fail to be detected in the lower basal and parabasal layers, except the EBNA.[63] The EBNA-1 has been proved to be observed in the nuclei of upper epithelial layers in 13 of the 16 OHL lesions, but is absent in the normal oral mucosa.[64] Another study analyzing RNA isolated from the OHL lesions showed the negative result of the *EBNA-1*, *EBNA-2*, or *EBNA-3A*, but positive result for the EBV lytic components.[65] Despite different results, the consistent findings so far have shown that there is a relatively scarcity of the latent proteins in the OHL lesions. Therefore, the distinct profile of gene expression in the OHL lesions from other malignancies may highlight their different natures, even though the EBV is known to possess the ability of oncogenesis. Similarly, there have been nearly no clinically reported cases of malignant transformation in the OHL lesions.

Interestingly, the elevated LMP-1 has been observed in oral squamous cell carcinoma (OSCC) and oral potentially malignant disorders (OPMDs).[66—68] Rahman et al.[66] found that the LMP-1 is expressed significantly higher in OSCC (59.67 %), followed by oral leukoplakia with dysplasia (34.15 %), oral leukoplakia without dysplasia (28.03 %), and normal oral mucosa (26.36 %).[66] Similar findings of overexpression of LMP-1 in OSCC (82.65 %) and OPMDs (69.46 %) with oral submucous fibrosis subgroup accounting the highest proportion were also reported in another study.[67] Regarding the site of OSCC, about a half of the EBV-positive OSCC and OPMD samples are excised from the tongue, and thus the association between the LMP-1 and the lesional site is statistically significant.[68] Therefore, even if there is limited evidence to prove the potential of malignant transformation in the OHL lesions, the above findings may somehow make the situation full of unexpected scenarios.

Conclusion

Since the OHL was first reported in 1984, there have been many studies to uncover the nature of this disease. However, 40 years after that, there are still unknowns. Therefore, we reviewed three different aspects of the OHL: (1) the necessity of presence of the EBV in the OHL lesions; (2) the OHL lesions in immunocompetent patients; (3) the potential of malignant transformation in the OHL lesions. The conclusions we made could be summarized as follows. First of all, the OHL can be clinically diagnosed but histopathological examination of the biopsy specimens with the confirmation of the presence of the EBV in the lesions can make the diagnosis more reliable, leading to a proper treatment. Secondly, the OHL is often seen in patients with the HIV infection or under other immunosuppressive states. Thus, the medical history is very important, and for those relatively healthy individuals with the suspicious OHL lesions, we should be devoted to find out the possibly insidious diseases or contributing factors for these OHL-like lesions. Finally, even if there is limited evidence to prove the potential of malignant transformation in the OHL lesions, there is still full of uncertainty and need further exploration.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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