Oral Hairy Leukoplakia in an HIV-Negative, Immunocompetent Patient

M. Moffat[a], S. Jauhar[b], M.E. Jones[c], D.G. MacDonald[b], D.H. Felix[b]

[a] *Birmingham Dental Hospital, Birmingham, UK*
[b] *Glasgow Dental Hospital and School, Glasgow, UK*
[c] *Edinburgh International Health Centre, Musselburgh, UK*

Summary: Oral hairy leukoplakia (OHL) is an Epstein-Barr virus-associated lesion, strongly associated with HIV infection. In recent years however OHL has also been described in iatrogenically immunosuppressed patients. Thus the lesion is no longer regarded as pathognomonic of HIV infection, but is related to immunosuppression in general. This report describes oral hairy leukoplakia in an HIV-negative immunocompetent patient using inhaled steroids.

Key words: hairy leukoplakia, immunosuppression, corticosteroids

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INTRODUCTION

Oral hairy leukoplakia (OHL), first recognised in 1984 (Greenspan et al, 1984), was described as a white proliferative oral epithelial lesion found on the lateral margin of the tongue. It was exclusively found in homosexual males, who were human immunodeficiency virus (HIV) seropositive. OHL has since been listed in the classification of oral lesions as a Group I lesion strongly associated with HIV infection. It has also been recognised in all risk categories for HIV infection (Classification and diagnostic criteria for oral lesions in HIV infection, 1993; Greenspan et al, 1986; Rindum et al, 1987; Ficarra et al, 1988). Furthermore, OHL is considered a marker of poor prognosis, as it frequently precedes the onset of acquired immunodeficiency syndrome (Greenspan et al, 1987).

In subsequent reports, it became apparent that this lesion is not pathognomomic for HIV infection, since OHL has been described in patients who are iatrogenically immunosuppressed. Some examples include bone marrow transplantation (Epstein et al, 1988; Birek et al, 1989) and solid organ transplantation (Itin et al, 1988; Greenspan et al, 1989), patients receiving cytotoxic chemotherapy for acute leukaemia (Syrjanen et al, 1989; Nicolatou et al, 1999), and those on systemic steroids (Schiodt et al, 1995) or topical steroid creams (Lozada-Nur et al, 1994). Thus OHL is regarded as a marker of immunosuppression. Notably, there have been several case reports of OHL in apparently immunocompetent patients (Felix et al, 1992; Eisenberg et al, 1992).

Clinically OHL presents as non-removable white patches with wide variation in size, severity and surface characteristics. Typically OHL is characterised by vertically corrugated white patch lesions on the lateral border of the tongue, of which two thirds are bilateral. Lesions on the ventral aspect of tongue have been reported, and lesions in this area have a smoother flat surface. Rarely it may affect the dorsum of the tongue and other sites.

Histological features include acanthotic parakeratinised epithelium, often with long, finger-like projections of parakeratin responsible for the corrugated clinical appearance. Acanthosis is present, and vacuolated cells with pyknotic nuclei and perinuclear clear halos (koilocyte-like cells) are found in the upper prickle layer. Candidal hyphae are present in approximately two thirds of cases, but notably there is an absence of a chronic inflammatory cell infiltrate in the lamina propria. The vacuolated cells are sites of EBV replication within the lesion, which is now recognised as the

causative agent of OHL and definitive diagnosis of OHL requires the demonstration of EBV within lesional tissue.

CASE REPORT

An apparently healthy 40-year-old woman presented for routine pre-employment screening. Her medical history revealed a history of asthma treated with beclomethasone and salbutamol inhalers. General physical examination was unremarkable. However, upon oral examination the presence of bilateral white patch lesions on the lateral aspect of her tongue was noted (Fig 1). The clinical features were consistent with OHL.

A detailed social history indicated that she had had five sexual partners during her lifetime. Her first husband had had frequent affairs and she acquired genital herpes prior to separation from him. She denied a history of drug abuse and had no concerns over HIV exposure.

In view of the above oral signs and following appropriate counselling, she agreed to be tested for evidence of HIV infection. The HIV antibody test was negative. Biopsies were taken from the lateral borders of the tongue and submitted for histological examination. The histological features were consistent with oral hairy leukoplakia. *In situ* hybridisation studies for EBV were positive thus confirming a diagnosis of OHL (Fig 2).

DISCUSSION

EBV, a herpes virus, has a predilection for circulating B-lymphocytes. Primary infection with EBV occurs early in life with a lifelong carrier state in the majority of individuals infected. These persons serve as a source of infection within the community. The main reservoir for the carrier state is thought to be circulating B-lymphocytes as well as epithelial cells in the oropharynx and salivary glands. EBV may be shed in saliva of asymptomatic individuals.

Reactivation of EBV and associated lymphoproliferative disorder are rare, demonstrating the effectiveness of normal host defences, which serve to limit such occurrences. Immune responses include interferon production, activation of T-suppressor cells, natural killer cells, and cytotoxic T cells as well as production of multiple EBV specific antibodies. The key role of the immune system in the prevention of EBV associated lymphoproliferative disease can clearly be demonstrated in those patients with specific immunodeficiency as well as those on immunosuppressive therapy.

It has been proposed that OHL is an opportunistic infection of the oral epithelium by EBV, in association with immunosuppression. It is believed to represent a viral replication lesion sustained by continued re-infection of surface epithelium by EBV in saliva.

Proposed theories to explain the site distribution on the lateral aspect of the tongue include the fact that the tongue is susceptible to trauma, allowing access of EBV in saliva to viral receptors in the prickle cell layers - in other words, auto-inoculation. In the case reported the most common causes of this lesion have been excluded by absence of HIV infection and general immunosuppression. It is therefore proposed that the OHL seen in this case may be related to local immunosuppression of the oral epithelium caused by the use of inhaled corticosteroids.

In view of the widespread use of metered dose corticosteroid inhalers in the management of respiratory disease and also oral mucosal disease, it is conceivable that EBV reactivation manifesting as OHL may be quite common, and this merits further study.

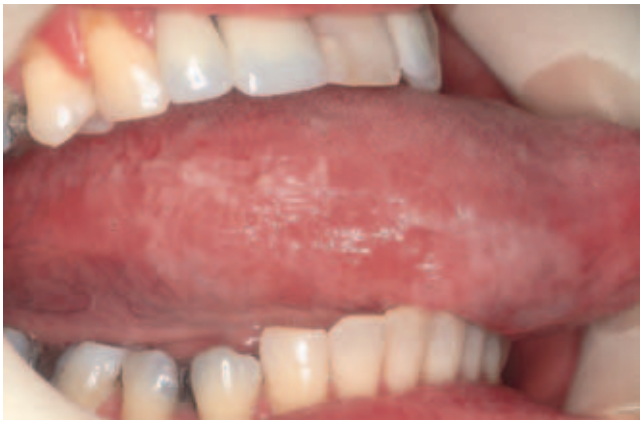

Fig 1 Clinical photograph of lesion.

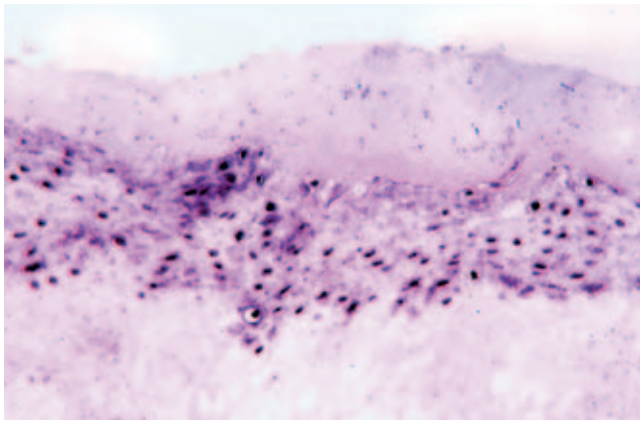

Fig 2 *In situ* hybridisation demonstrating EBV DNA within lesional tissue.

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Reprint requests:
D. H. Felix
Consultant in Oral Medicine
Glasgow Dental Hospital and School
378 Sauchiehall Street, Glasgow G2 3JZ
Tel: 0141 211 9654
E-mail: David.Felix@nes.scot.nhs.uk

Following submission of this manuscript Professor MacDonald died in December 2005.