HAIRY LEUKOPLAKIA

Definition

Oral hairy leukoplakia (OHL) was first observed in 1981 and reported in 1984 as a common, benign, asymptomatic, white, non-removable lesion of the lateral borders of the tongue in patients with HIV infection and AIDS. The lesion is rare in the healthy population. In patients with HIV infection, when laboratory estimates are not available, OHL may be a useful clinical marker of the presence, severity and progression of HIV disease. Since its first description, OHL has been observed in immunodeficient patients with other causes of immunosuppression (chemotherapy, long term steroid use, organ transplantation). Thus, it is regarded as a clinical marker of impaired immune status, in general, and its appearance should prompt the clinician to carry out further investigations in order to establish the underlying cause of immunosuppression. Furthermore, OHL has an intimate etiologic relationship with Epstein-Barr virus (EBV) which replicates floridly within the lesion. Thus, in addition to its clinical significance, OHL has a unique biologic importance offering a unique in vivo research model for the study of the Epstein-Barr virus.

Epidemiology

Reported prevalence rates of OHL vary considerably according to the clinical criteria used and the characteristics of the study population such as the type of immunosuppression, risk group for acquisition of HIV disease (homosexual, hemophiliacs etc), clinical stage of the patients etc. On average, in the early periods of the HIV pandemic, it was seen in one quarter of HIV-infected patients. With the passage of time, the understanding of the pathogenesis of HIV disease was improved and new drugs were developed to combat the infection. Medication has changed from monotherapy to current triple combination therapy (Highly Active Anti-Retroviral Therapy;HAART), which resulted in a dramatic improvement of all virological and immunological parameters of the patients and subsequently to a decrease in the prevalence of HIV-associated oral lesions as compared to earlier periods. Thus, the current incidence of OHL has dropped from 25% to less than 10%. There are very few reports of the occurrence of OHL in immunocompetent subjects, but these lesions do not contain EBV.

Clinical presentation

Oral hairy leukoplakia presents as unilateral or more often bilateral, adherent, white or gray patches mainly on the lateral lingual margins and sometimes the dorsum or ventrum of the tongue. The surface of the patches has usually a corrugated appearance forming prominent folds or projections (sometimes so marked as to resemble "hairs", hence its name). When chronic, these alterations assume a more homogenous appearance similar to that of idiopathic leukoplakia. When seen at the ventral surface of the tongue, the lesion may be flat. OHL may occur (rarely) on other mucosal surfaces such as buccal mucosa, floor of the mouth and soft palate. OHL has so far not been observed in other areas than the oral. Although usually symptomless, it may cause a burning sensation, while patients may complain of its unsightly appearance, especially when it is extended on all lingual surfaces.

Aetiopathogenesis

Though the pathogenesis has yet to be elucidated in detail, its cause is currently thought to be a specific EBV infection facilitated by immunodeficiency. EBV is acquired by over 90% of the world population during childhood or adolescence and thereafter remains in a carrier state for the lifetime of the infected host. The virus is shed in saliva and cellular EBV receptors are found in the upper layers of parakeratinized oral epithelium. The close relationship between EBV infection and OHL is evident since EBV antigens have been demonstrated in tissue sections by immunohistochemical analysis and EBV-DNA has been demonstrated in tissue by molecular techniques such as Southern blotting and in situ hybridization (ISH). Intracellular herpes virus particles have also been observed by electron microscopy. Experiments have shown that the epithelial hyperplasia observed in OHL is directly related to the combined action of EBV proteins, which delay the death of the oral epithelial cells allowing very intense viral replication without themselves undergoing lysis. Extensive molecular studies have demonstrated that several EBV variants may be present within a single lesion, the infecting types may change over time, strain recombinations may also occur but whether the newly created strains lead to or are consequential to OHL is unclear. Also unclear is how OHL is initiated and whether it develops after EBV reactivation from latency state or is a result of superinfection of upper epithelial cells by the virus derived from saliva or other infected cells. Also, the mystery of why OHL is localized mainly on the lateral borders of the tongue has not been adequately clarified.

Diagnosis

Generally, the clinical features alone (as described above), the lack of response to anti-fungal therapy, combined with other signs of immune dysfunction and the social and medical history of the patient should provide clues to the provisional diagnosis of OHL. Histological examination is indicated only when clinical features are vague. Epithelial hyperplasia with hyperparakeratosis and acanthosis are consistent features of OHL together with koilocytosis with pyknotic nuclei and perinuclear halos in the prickle cell layer, intranuclear inclusions, paucity or absence of Langerhans cells and a sparse inflammatory cell infiltrate in the lamina propria. It is important to note that in many cases of OHL there may be a supervening fungal population that should not be overlooked or mistaken as oral candidosis.

However, the histologic changes are not specific to OHL, thus, the demonstration of EBV is essential to the definitive diagnosis of OHL. Demonstration of EBV in histological or cytological specimens by mean of molecular techniques or electron microscopy is needed for the definitive diagnosis of OHL. Exfoliative cytology is a useful alternative to incisional biopsy, for which there are often contraindications (e.g., patients with bleeding disorders, children, or severely debilitated patients). Although, in clinical practice, the need to definitely diagnose presumed OHL seldom arises, it is important to differentiate it from other oral lesions that may have a similar clinical appearance. Correct early diagnosis can facilitate the establishment of the underlying immunodeficiency. The differential diagnosis should include idiopathic leukoplakia, smoker's keratosis, frictional keratosis, hyperplastic candidiasis, lichen planus, lichenoid reaction etc.

Treatment

Since OHL is usually symptomless and has no known premalignant potential, treatment is seldom required. It tends to clear with HAART. Several treatment options are available for symptomatic lesions, such as topical retinoids, topical podophyllin, surgical excision and cryotherapy, but none prevent the recurrence of the lesion after therapy. Antifungal therapy may lead to some reduction in the extent of the lesion but does not eradicate the infection. Antiviral agents can result in amelioration of OHL, but lesions recur soon after discontinuation of therapy while side effects may occur and resistant viral strains may arise. Furthermore, it has been documented that OHL improves spontaneously in about 10% of the cases.

Prognosis and complication

No cases of malignant transformation in patients with preexisting OHL have been reported, although mild cellular atypia has been described. Patients might complain for its unsightly appearance, in which cases, therapeutic intervention might be indicated. OHL can be an early, if not, the first sign of HIV infection. OHL can be used as a convenient clinical marker of HIV-disease severity, since most affected patients have CD4(+) T-cells counts < 400/mm^3. In addition, OHL has a reliable prognostic value in the natural history of HIV disease. The estimated rate of progression to AIDS at one year for subjects with OHL varies from 10% to 48% and at two years from 24% to 63%. Patients with OHL are also more likely to develop lymphomas.

Prevention

Immunosuppression is a precondition for the development of OHL. HIV infection dramatically enhances the risk of its appearance, but why this is so remains puzzling. The improvement of immunological status of HIV-infected patients with the HAART therapy has dramatically reduced the frequency of OHL.

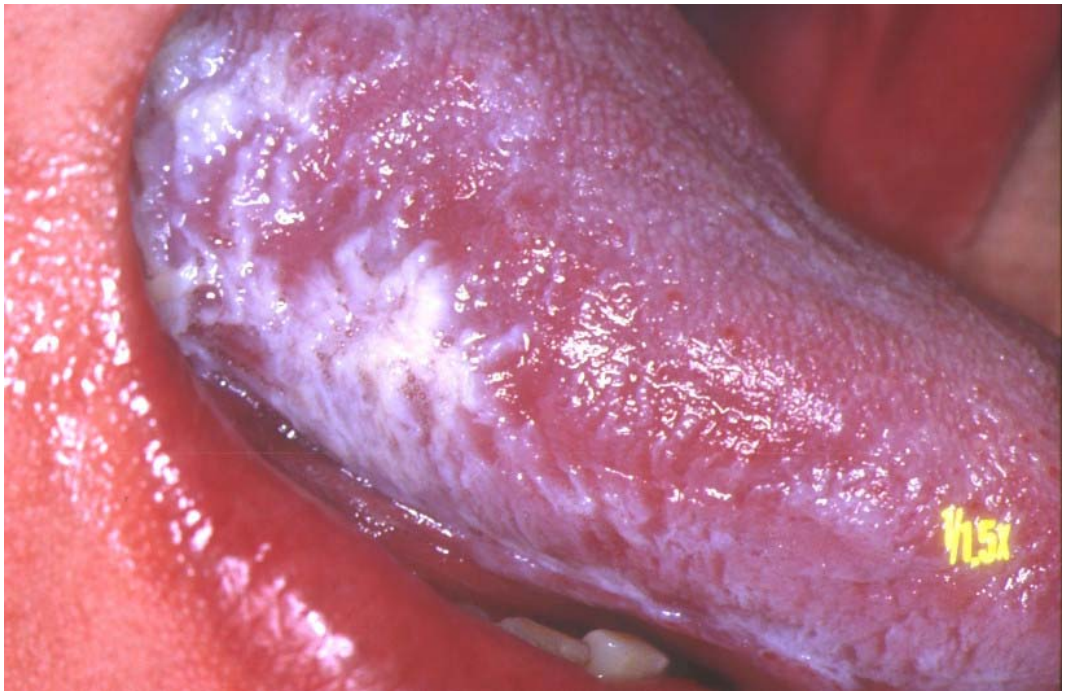

Figure 1. Hairy leukoplakia of the border of the tongue

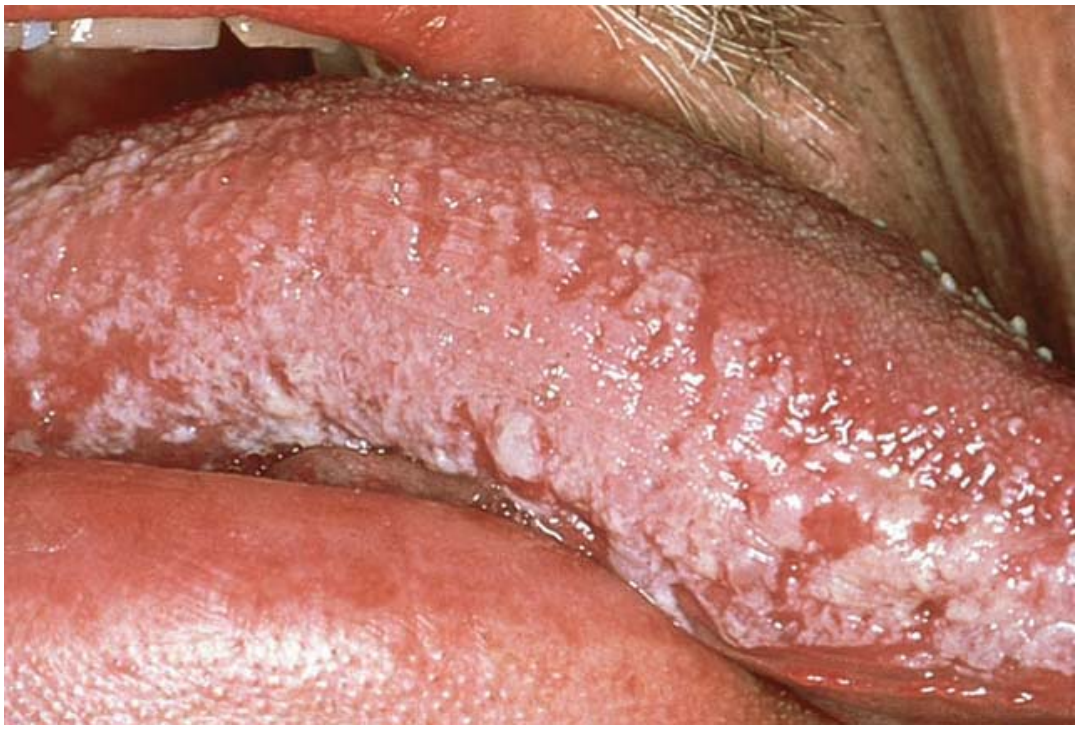

Figure 2. Hairy leukoplakia of the border of the tongue

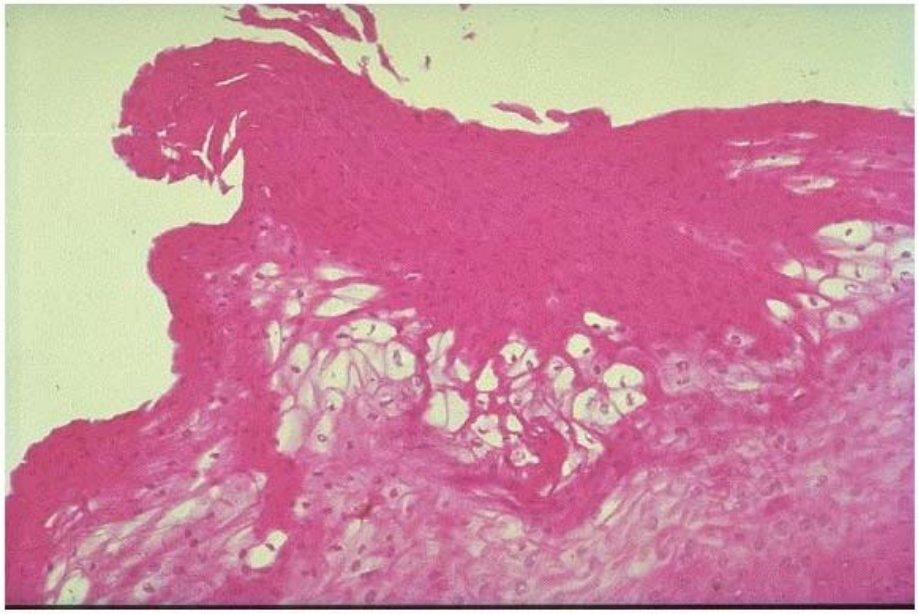

Figure 3. Hairy leukoplakia, histological aspect, showing hyperparakeratosis and pyknic cell nuclei (koilocytosis) indicating presence of virus (courtesy: prof JJ Pindborg, Copenhagen)

Further reading

1 Epstein JB, Fatahzadeh M, Matisic J, Anderson G. Exfoliative cytology and electron microscopy in the diagnosis of hairy leukoplakia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995; 79:564-9.

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3 Webster-Cyriaque J, Middeldorp J, Raab-Traub N. Hairy leukoplakia: an unusual combination of transforming and permissive Epstein-Barr virus infections. J Virol 2000; 74:7610-8.

4 Palefsky JM, Berline J, Greenspan D, Greenspan JS. Evidence for trafficking of Epstein-Barr virus strains between hairy leukoplakia and peripheral blood lymphocytes. J Gen Virol2002; 83:317-21.

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