Oral hairy leukoplakia: observations in 95 cases and review of the literature

Peter A. Reichart[1], Angelika Langford[1], Hans R. Gelderblom[2], Hans-Dieter Pohle[3], Jürgen Becker[1], Hans Wolf[4]

[1]Abteilung für zahnärztliche Chirurgie/ Oralchirurgie – Nord – Freie Universität Berlin, [2]Robert Koch-Institut des Bundesgesundheitsamtes, [3]II. Innere Abteilung, Universitäts-Klinikum Rudolf Virchow, Berlin and [4]Max-von-Pettenkofer-Institut, Munich, West Germany

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Oral hairy leukoplakia (HL) was observed in 25.4% of 373 HIV-seropositive patients (n = 95). 87 were men of an average age of 37.1 yr, 8 were women (30.3 yr). 71.6% of the patients were male homosexuals. At initial diagnosis of HL the majority of cases was classified as CDC IVc_1 (45.3%) and CDC II (22.1%). Average CD4/CD8 ratio (n = 19) was 0.24 with a range of 0.04–1.0. Thirty biopsies of HL revealed some of the histologic features thought to be characteristic. In only 20 of 30 biopsies EB-virus-specific-capsid antigen was detected. The problems of clinical and histological diagnosis of HL are discussed. Further strict criteria are necessary in order to define HL more distinctly.

Key words: HIV infection; Epstein-Barr virus; leukoplakia, hairy.

P. A. Reichart, Abteilung für zahnärztliche Chirurgie/Oralchirurgie (Nord), Freie Universität Berlin, Föhrer Str. 15, D – 1000 Berlin 65, West Germany

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Three years after the first patients with acquired immunodeficiency syndrome (AIDS) were reported in 1981, oral hairy leukoplakia (HL) was described (1).

Clinical features and epidemiology

Oral hairy leukoplakia is clinically characterized as a white lesion of the lateral border of the tongue, occasionally also occurring in the buccal mucosa with slightly raised, poorly demarcated and corrugated "hairy" surface. Lesions cannot be rubbed off and are reported to be usually symptomless. Hairy leukoplakia has so far not been observed in other mucosal areas than the oral (2). During recent years a number of HL cases either as case reports or larger series have been reported from various areas of the USA, Europe and Africa (3–20).

While HL was initially observed in male homo- or bisexual men, it has now been shown to occur, though less often, in all HIV risk groups: hemophiliacs (4, 8, 21), drug abusers (6, 10, 17), blood transfusion recipients (21) and female partners of HIV-infected men (21). Recently, HL has been described in an HIV-negative patient with acute myeloblastic leukemia (22) and an HIV-negative renal transplant patient (23), suggesting that HL is not a specific lesion associated to the HIV-infection, but may be a sign of immunosuppression in general.

Prevalence rates of HL vary considerably. Four out of 23 patients with antibodies against HIV revealed HL (17.5%) (24). Among 115 HIV-seropositive patients 13% revealed HL (25). Among HIV-seronegative male homosexuals (n = 492) 1% demonstrated HL (25). Of a total of 375 homosexual men 28% had developed HL; it occurred in 23% of the AIDS cases, in 9% of the ARC cases and 47% in high risk persons (9). In a study from Berlin, 26% of ARC patients had HL (6). In Copenhagen, 32% of 69 seropositive asymptomatic patients, 36% and 46% of ARC and AIDS patients revealed HL (26). Low prevalence rates were reported from New York (5%) and Frankfurt (4.8%) (28). None of 30 hemophiliac patients with factor VIII or IX deficiencies revealed HL (29). In contrast, 23 of 120 consecutive patients belonging to the i.v. drug abusing risk group (19%) had developed HL (17). In a study on oral manifestations of AIDS in Tanzania 35% of 58 patients had developed HL. The male: female ratio in this cohort was 1.6 : 1.0 (20).

The average age of HIV-infected patients with HL showed some variation. The average age of i.v. drug abusing Italian patients was 25 yr (range 20 to 50 yr) (17). In contrast, the average age of male homosexual patients (n = 50) was 38 yr (range from 25 to 53 yr) (13), 36.6 yr (range 24 to 51 yr) (8) and 36 yr (range 22 to 65 yr) (9). Duration of HL ranged from 1 to 64 months with a mean of 13 months in a study of 50 cases with HL (13).

The clinical features of HL vary considerably. 70% of patients with HL had bilateral lesions. The total area of HL lesions ranged from 14 to 4200 mm^2 with a mean of 814 mm^2. The degree of intensity of HL was mild in 40% of the cases, moderate in 52 and severe in 8%

(13). While flat lesions were usually located on the inferior surface of the tongue, the more corrugated hairy lesions were observed on its lateral border (13). There is no apparent association between the size and intensity of HL and the relative risk for subsequent development of AIDS (30). While most studies have stated that HL is rather symptomless, burning sensation of tongues with HL even after antimycotic therapy has been described (28). The relation of HL to infection with HIV and the risk of developing AIDS has been studied. Of 155 patients examined 12 had AIDS at the time of diagnosis the syndrome developing in an additional 43 patients in 1 to 31 months. Survival analysis showed that the probability of AIDS developing in patients with HL was 48% by 16 months and 83% by 31 months. As such HL was considered to be a predictor of the development of AIDS (31). In this context it is noteworthy that HL has been included in the group of secondary infectious diseases (group IV, subgroup C, category C-2) of the CDC surveillance case definition (32).

Histopathology

In their original description of HL GREENSPAN *et al.* (1) stated that the histopathology of HL was similar to that of the flat wart of the skin. The following criteria were proposed: 1: keratin projections 2: some degree of parakeratosis and acanthosis. 3: characteristic ballooning of cells in the prickle cell layer (pyknotic nuclei and perinuclear halos); these changes were compared to koilocytosis as described in dermal warts and uterine condylomata. 4: little or no inflammation. 5: mild epithelial atypia in some cases.

Most researchers describing histopathologic features of HL followed the proposed criteria. Koilocytosis, however, has been used when describing cells with pyknotic or crenated nuclei with voluminous cytoplasm with faint eosinophilia (8), as koilocytoid cells (12), as large, pale staining cells similar to koilocytes as described in uterine condylomata (15), as cells which had undergone cytopathic changes revealing a ground glass nucleus with basophilic nuclear inclusions, ballooning of cytoplasm and intracellular edema (33), as well as vacuolated cells resembling koilocytes (13). It has been stated that parakeratosis and subcorneal koilocytosis are not specific for HL since these findings have also been observed in candidiasis and leukoplakias (8). In a recent study of histologic features of 40 HL cases hyperparakeratosis was observed in 100%, hyperplasia/acanthosis in 80%, hair-like projections in 80%, koilocytosis in 98% and lack of inflammatory infiltrate in 78%. The absence of Langerhans cells in HL has been considered to be an important factor in the pathogenesis of HL (38). Not all lesions exhibit all microscopic characteristics as described in the first report (13).

The role of *Candida* infection in HL was of considerable interest because initially *Candida* infection was supposed to be an underlying cause of HL (1). Larger series of HL cases in which oral smears for *Candida* were taken showed varying percentage of positive smears: 70.3% (3), 58.8% (2), 50.7% (31), 26.1% (17). Demonstration of hyphae in PAS sections revealed presence of Candida in: 100% (12), 66.7% (13), 50% (18), 49.3% (3), 46.7% (1), 46.2% (19), 43% (13).

Immunohistochemistry

DNA hybridization studies with Epstein-Barr virus (EBV) probes in Southern blots demonstrated EBV DNA in epithelial cells of HL (3). Other immunohistochemical studies using in situ hybridization to detect EBV DNA confirmed the presence of this virus in HL (16, 33, 34). However, it must be stated that EBV DNA was also found in an HIV-1-seronegative patient (16). Using semithin cryosections in conjunction with the APAAP staining technique, EBV capsid as well as nuclear antigen of EBV was demonstrated in cases of HL (35). While the presence of HPV was stated using immunohistochemical methods and electron-microscopy in the first reports on HL (1, 3) it was not revealed in subsequent studies. HIV structural proteins were detected using immunohistochemistry (36).

Electron microscopy

Electron microscopic studies have revealed the presence of herpes type virus with clusters of nucleocapsids located in nuclei and enveloped complete particles occurring in the cytoplasm and extracellular spaces (1, 11, 12, 15, 17, 18, 35). In addition, tubuloreticular structures as well as membrane differentiations were revealed in HL (12, 35). Cristalline inclusions in epithelial cells of HL have recently been described (37).

Treatment

While most investigators do not consider HL to be a clinical condition which requires therapy, some reports on the effect of treatment have been published. Thus, HL has been shown to disappear during acyclovir therapy (7, 19) and resolution has occurred following therapy with DHPG (39), another nucleoside analogue, topical vitamin A acid (28) and following azidothymidine therapy (AZT) (4, 27). After discontinuation of therapy recurrence was observed in all responders.

Material and methods

During a period of 5 yr 373 HIV-seropositive patients (326 men, 47 women) of an average of 36.2 years were examined for the presence of HL (CDC II: 25%, CDC III: 9%, CDC IVa: 12%, CDC IVb–e: 54%). Clinical diagnosis was based on the presence of white, non-removable patches on the lateral border of the tongue in accordance with the original description of HL (1). In cases of oral candidiasis involving the HL lesion, either a topical (miconazole) or systemic antimycotic treatment (ketokonazole) was administered. The diagnosis of HL was made in those cases where a whitish lesion at the lateral border of the tongue persisted after a minimum of 10 days in spite of this antimycotic regimen. A number of parameters were recorded: 1: sex. 2: age. 3: risk group. 4: period of observation. 5: CDC-classification. 6: CD4/CD8-cell ratio. 7: regression in relation to therapy. 8: deaths occurring during observation. 9: smears for oral candida infection.

In addition, biopsies of HL were taken from 30 patients. Specimens were divided and one part was fixed in formalin for routine histology (H & E, PAS). The other part was deep frozen in liquid nitrogen. For the immunohistochemical detection of EBV-capsid antigen (EBV-VCA, BcLF1 p150) cryostat sections of 3–4 μm were air-dried for 2 h and fixed in acetone for 15 min at room temperature. Sections were first incubated with primary monoclonal antibody against EBV-VCA (dilution 1 : 2000), followed by the unlabelled goat-anti-mouse bridging antibody (dilution 1 : 60; Jackson, Avondale, USA) and finally with the

Table 1. Risk groups for 95 patients with HL.

Risk factors	Men: $n = 87$	Women: $n = 8$
Homosexual	71	1
i. v./homosex.	3	
i. v. drug user	9	7
Hemophiliac	2	
Transplant pat.		1
Unknown	2	

alkaline phosphatase-mouse-anti alkaline phosphatase (APAAP) immune complexes (dilution 1 : 50; Dianova, Hamburg, FRG) (35).

Results

Of a total of 373 HIV-seropositive individuals 95 patients revealed HL clinically (25.4%). In 75% HL was bilateral. HL in extralingual sites was not seen. Clinically, HL varied in appearance. A corrugated pattern ($n = 80$) as well as whitish plaque-like lesions ($n = 15$) (16%) extending on to the sublingual surface was observed. Hair-like projections were rarely seen. In 17% of patients HL covered an area of up to 15 mm in diameter. None of the patients really complained about the lesion. More than 75% of patients, especially homosexual men, were aware of their lesion, had heard about its significance and usually were those who refused to have biopsy taken. Average age of the male patients was 37.1 yr (range 19 to 82 yr), of the female patients 30.3 yr (range 26 to 46 yr). 87 patients were men, 8 were women. The majority of the male patients were homosexual men ($n = 68$) (71.6%). Risk factors for 95 patients with HL are shown in Table 1. 9 men and 7 women were i.v. drug abusers (16.8%). 14 homosexual men (average age 49.9 yr, range 39–82 yr) with HL had died after an average period of observation of 7.2 months (range 1 to 27 months). 13 patients with HL have been observed more than 4 wk with an average of 5.2 months (range 1 to 13 months). In 68 patients the period of observation was less than 4 wk. Out of 95 patients with HL 18 had no general symptoms, 17 presented with ARC and 60 had developed AIDS. The CDC classification at the initial diagnosis of HL in 95 patients is shown in Table 2.

CD4/CD8 ratios at the time of initial diagnosis of HL could be stated in 19 patients revealing an average of CD4/CD8: 0.24 with a range from 0.04–1.0. The absolute number of CD4 cells was : 149 mm^3 (range 10–470) (average IgA : 270 (134–380); average IgG : 1690 (1100–2400), average IgM : 243 (149–374). A total of 13 patients with HL received AZT. In seven patients HL regressed clinically; two of these patients developed resolution of HL during acyclovir therapy, one patient showed regression under HOE/Bay 946 therapy and in one case the regression did not coincide with a particular treatment.

In 31 patients with HL without previous antimycotic treatment smears for *Candida albicans* were taken. Of these, 14 smears were positive for C. albicans. When diagnosis of HL was stated 79% of patients showed clinical symptoms of oral *C. albicans* infection, 22% suffered from periodontal lesions of RPP and/or NUG, and 8% of oral Kaposi's sarcoma. In 18% of patients HL was the only oral manifestation of HIV infection.

Histologic and immunohistochemical findings are summarized in Table 3. Hyperparakeratosis (100%), acanthosis/hyperplasia (100%), relatively few hair-like projections (33%) and koilocyte-like cells (90%) were found. Absence of inflammatory changes was also observed (53%). In PAS-stained sections candidal hyphae in epithelium were found in 47%. Immunohistochemically, EBV-capsid antigen (VCA) was only detected in 20 out of 30 biopsies. A strong nuclear immunolabelling was found in cells of the upper stratum spinosum and in the ballooned, koilocyte-like epithelial cells (Fig. 1). Staining was often not continuous over the whole section and large areas, which showed the same histologic characteristics as areas with an intense immunolabelling did, were essentially negative for VCA (Fig. 2).

Discussion

The largest group of individuals suffering from AIDS in the Federal Republic of Germany including West Berlin are homosexual men (40). This is the risk group with a high prevalence rate of HL, as has been found in the present study. Although the prevalence rate showed significant differences some centers (San Francisco, Copenhagen) have recorded comparable prevalence rates (25.4%). Also the data for average age and range were very similar. In contrast, i.v. drug abusing HL patients (16) appear to be considerably younger (27 years). Larger studies of cohorts of i.v. drug abusers with HL compared to homosexual/bisexual males are necessary in order to reveal differences in the development and course of HL. The short period of observation of HL (68 patients less than 4 wk) does not allow to draw any conclusions on the development of HIV-infection in patients with HL. It must also be stated that in this cohort the majority of patients were classified as CDC IVb, IVc, IVd or IVe (AIDS cases 54%). Of considerable interest is the CD4/CD8 ratio and the development of HL. In HIV periodontitis a clear-cut relation between the decrease of the number of CD4 cells as well as in CD4/CD8 ratio has been found (J. Winkler, personal communication). It would be of interest to see when and at which CD4/CD8 ratio HL is first observed.

Therapy of HL does not seem to be of major priority. In most cases HL was symptomless and exclusive treatment of HL lesions was never necessary. Acyclovir as well as AZT therapy resulted in clinical disappearance of HL lesions, as has been observed in other studies (6, 28, 39). As could be suspected in cases of immunodeficiency, recurrences occurred.

Table 2. Initial CDC classification of 95 patients with HL.

CDC group	*n*	%
CDC II	21	22.1
CDC IV	12	12.6
CDC IVa	2	2.1
CDC IVb	1	1.1
CDC IVc_1	43	45.3
CDC IVc_2	2	2.1
CDC IVd	13	13.5
CDC IVe	1	1.1

Table 3. Histologic findings in 30 biopsies of HL.

	n
EBV-VCA+	20
Hyperparakeratosis	30
Hyperplasia/acanthosis	30
Hairlike projections	10
Koilocyte-like cells	27
Bacteria on surface	11
PAS+; (Candida)	14
Leukocytes in rel. to *Candida*	0
Leukocytes in epithelium	10
Inflammation absent	16
Superf. slight diffuse infl.	9
Superf. small clusters	5

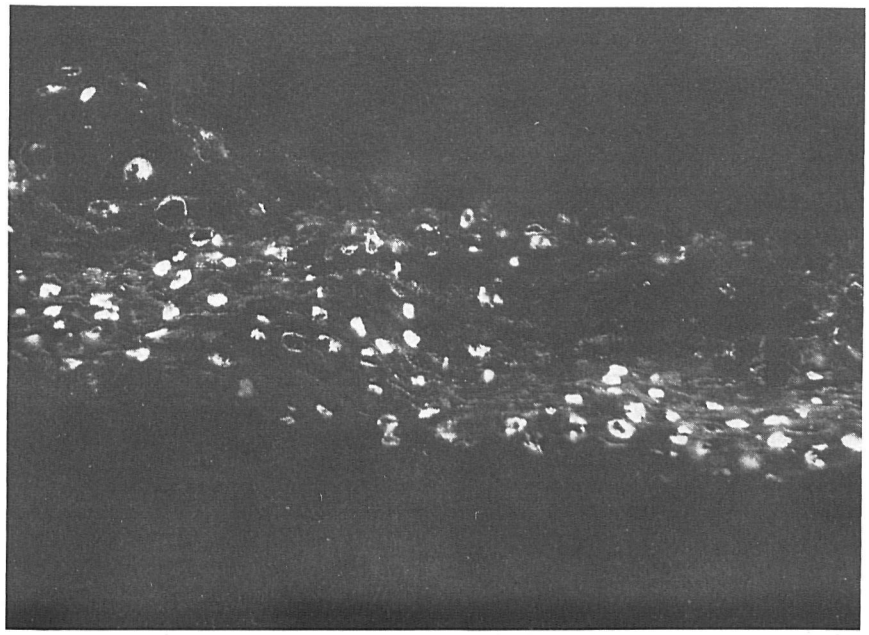

Fig. 1. Immunohistochemical detection of EBV-VCA in surface epithelium with even distribution of positive epithelial cells (FITC, EBV-VCA; × 510).

Although a considerable number of cases with HL have been published, problems relating to clinical and histologic diagnosis and of pathogenesis have not been solved.

Clinical diagnosis of oral hairy leukoplakia

White lesions of the oral mucosa are common and a number of differential diagnoses have been summarized as frictional keratosis, lichen planus, galvanic lesion, idiopathic leukoplakia, tobacco-associated leukoplakia, tongue biting, severe leukedema and geographic tongue (13). A most important issue in the diagnosis of HL is the question whether the diagnosis is based on information on HIV-seropositivity or -negativity. As soon as a clinician is informed about the HIV status of a patient he is inclined to assess a lesion on the border of the tongue as HL. In addition to this bias the problem of oral candidiasis involving the lateral border of the tongue must be considered. Only after antimycotic therapy should a diagnosis of HL be made. The fact that HL also occurs in non-HIV-infected individuals (34) makes the diagnosis of HL even more complicated.

Histopathologic diagnosis

Although clear-cut histopathologic criteria have been proposed, a number of problems are still existent and have been addressed recently (13, 18, 34). As in clinical diagnosis, the situation of bias is also present for the oral pathologist. The diagnosis of HL will readily be made if some of the criteria characteristic for HL are present in a biopsy of the lateral border of the tongue and if the status of HIV infection of a patient is known. In most countries, biopsy specimens or smears have to be signed out to be infectious or to contain HIV-infected material. In contrast, it appears to be extremely difficult to make a diagnosis of HL in cases of HIV-seronegative patients. Histologic criteria of HL may not always be present in all cases (12). In addition to this, some of the criteria are of doubtful value, particularly in relation to: 1: hyperparakeratosis. 2: hyperplasia/acanthosis. 3: keratin projections. 4: koilocytosis. 5: presence of EBV in biopsy material.

To the present date we are not aware of any orthologic study of the macro- and microstructure of the lateral border of the tongue. Preliminary studies showed, however, that normal tongues reveal a corrugated pattern at the lateral border which, however, is not white as in HL (Lis Andersen *et al.*, in preparation). In this context it is questionable whether hyperparakeratosis as described for HL is an abnormal histologic criterium for the microstructure of the lateral border of the tongue. This is the area of the tongue which is in constant contact with the teeth and therefore, as a sign of increased epithelial turnover due to microtrauma, some degree of hyperparakeratosis may normally occur. The same relates to hyperplasia and acanthosis. Studies of both the macro- and the microstructure of the lateral border of the tongue in non-HIV-infected patients between the age of 20 and 45, preferably men, are urgently needed. Keratin projections have been observed in the majority of the cases (80%) (13), however,

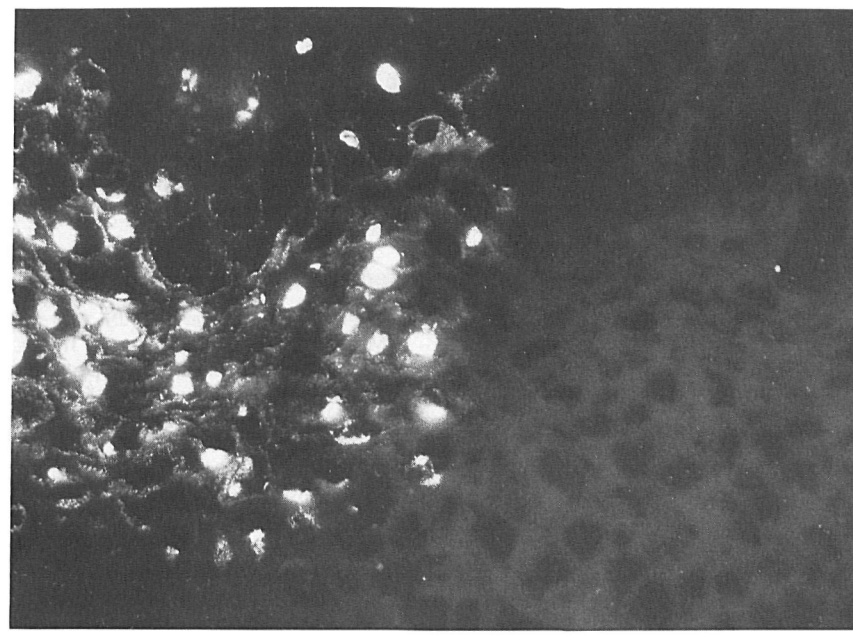

Fig. 2. Surface epithelium shows positive staining for EBV-VCA on left side of print. Border between positive and negative areas is abrupt (FITC, EBV-VCA; × 700).

they are missing in about 20% of diagnosed HL cases. Clinically, as well as histologically, these keratin projections or hair-like formations have not been observed in our material (33.3%) as frequently as it has been reported in other studies.

The concept of koilocytosis in HL has also been questioned recently (18, 34). Originally, this particular change has been described in uterine cervical mucosa (41). Human papillomavirus (HPV) has been considered to be the underlying cause of koilocytosis in cervical mucosa. In HL HPV, however, has to date not convincingly been demonstrated. The fact that some researchers have used the term 'koilocyte-like changes' is a hint towards a differentiated understanding of the concept of these changes. EBV has undoubtedly been demonstrated in HL and has been discussed in the etiology of this lesion. According to SYRJÄNEN *et al.* (34) the vacuolized or ballooning epithelial cells found in HL are not identical with the true "koilocytes". The characterization of these large pale staining cells in the prickle cell layer of HL is even more complicated by the fact that such cells may also be observed in oral mucosa affected by candidiasis and in oral parakeratotic leukoplakias (8). Enlarged epithelial cells of the surface layers may also occur in lesions such as tongue biting. It is unknown whether koilocyte-like cells also occur in the normal oral mucosa of the lateral border of the tongue.

Due to the insecurities which may occur in the histopathological diagnosis of HL SYRJÄNEN *et al.* (34) have suggested that in patients whose HIV antibody status is unknown the presence of EBV in lesions should be demonstrated immunohistochemically or using DNA techniques. Although this procedure may help in clarifying the diagnosis of HL, it must be considered that EBV has now also been demonstrated in oral mucosa other than that of the lateral border of the tongue (33). In particular the demonstration of structural proteins of EBV (capsid antigen) in superficial layers of oral epithelium would be helpful in the histopathological diagnosis of HL. However, due to the spotty distribution of EBV expression in oral epithelium, VCA may not be demonstrated if biopsies are too small or non-representative as was found in the present study where EBV could only be found in 20 out of 30 biopsies. It appears from the present knowledge that comparative studies of the normal lateral border of the tongue are necessary in order to reassess the various histological criteria used for the diagnosis of HL.

Etiology, pathogenesis

The detailed etiology of HL is unsolved. Several factors have been suggested to play a role in pathogenesis. Initially, *Candida* infection had been considered to be the cause of HL (1). In fact it must be stated that even after antimycotic therapy a high number of biopsy specimens (14 of 30) revealed hyphae in PAS-stained sections. In EM studies the presence of both *Candida* and EBV particles in oral epithelium has been demonstrated (35). The role of both *Candida* and EBV in producing a whitish lesion at the lateral border of the tongue has not been solved. In fact, our observation of HL-biopsies negative for EBV antigen may hint to HL as a condition for EBV expression rather than EBV as a cause of these lesions.

Although the absence of Langerhans cells at the lateral border of the tongue has been discussed in the pathogenesis of HL (38) it is not clear why HL predominantly involves the lateral border of the tongue. It has recently been shown that Langerhans cells represent a susceptible substratum for HIV-1 replication also serving as reservoir for HIV (42).

While HL appears to be a newly recognized oral disease entity a number of problems are still unsolved. These relate to global epidemiology, clinical and histologic diagnosis, to etiology as well as pathogenesis. In all these fields, further studies are needed.

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