

ORAL LESIONS AMONG HIV-INFECTED HEMOPHILIACS. A STUDY OF 54 PATIENTS

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ABSTRACT

Background. HIV-infected individuals develop a large variety of oral manifestations. This study was designed to assess the prevalence and types of oral lesions among HIV-positive hemophiliacs.

Materials and Methods. A study population of 54 hemophiliacs was evaluated from February, 1987 to March, 1992 in order to analyze types, prevalence and relationships to clinical stages of HIV-related oral lesions. Thirty-six (67%) of the group of patients were HIV-seropositive. The remaining 18 tested negative to HIV during the observation period.

Results. The majority of patients suffered from hemophilia A. One patient was also bisexual and two were also intravenous drug abusers. Analysis of patient stage revealed that half had a CD4⁺ T-lymphocyte count over $0.5 \times 10^9/L$ cells, 10 between 0.2 and $0.499 \times 10^9/L$ and 8 showed a count lower than $200 \times 10^9/L$. Oral lesions were recorded in 18 (50%) HIV-seropositive hemophiliacs. No oral lesions were observed among the HIV-seronegative hemophiliacs. Advanced stage of immunosuppression and presence of oral lesions were significantly associated ($p=0.040$). Candidiasis was the most common disturbance, followed by hairy leukoplakia. Oral herpes simplex infection, necrotizing gingivitis and facial herpes zoster were found in a small number of patients. Those with oral lesions showed a lower median CD4⁺ T lymphocyte count ($0.209 \times 10^9/L$ cells; range 0.008 to 0.615) when compared to the ones without oral lesions (median CD4⁺ count was $0.539 \times 10^9/L$ cells; range 0.042 to 1.180; $p=0.002$).

Conclusions. HIV-seropositive hemophiliacs may develop oral lesions during the course of their disease. Candidiasis and hairy leukoplakia are among the most common manifestations. A careful oral examination should be included in the clinical evaluation of all HIV-infected hemophiliacs.

Key words: HIV, AIDS, hemophilia, oral cavity, oral candidiasis

Oral lesions (OL) are common early signs of infection with human immunodeficiency virus (HIV). Oral candidiasis (OC), hairy leukoplakia (HL), Kaposi's sarcoma, periodontal lesions and infections with herpes viruses are frequently observed in HIV-infected patients.¹⁻⁶ These oral manifestations have been studied mainly in HIV-infected male homosexuals and intravenous drug abusers.^{2,3,5,6} Few studies have reported on the prevalence and clinical characteristics of these lesions in

hemophilic populations.⁷⁻¹²

The purpose of this study was to assess the prevalence and types of oral lesions among a population of HIV-seropositive and HIV-negative hemophiliacs.

Materials and methods

Our study population consisted of 54 male hemophiliacs who were observed at the Institute of Odontology and Stomatology of the

Table 1. Categories of 36 HIV-seropositive hemophiliacs.

<i>patient groups</i>	#	%
Hemophilia A	24	67
Hemophilia B	9	25
Hemophilic & IVDA	2	5
Hemophilic & bisexual	1	3
Total	36	100

University of Florence and USL 10/D from February 1987 to March 1992. Thirty-six (67%) of them were HIV-seropositive. The remaining 18 (33%) tested negative to HIV during the observation period. Seropositivity was evaluated in all patients by the HIV-antibody test (Elisa), followed by Western blot analysis for confirmation. For the HIV-seropositive subjects the median observation period lasted 33 months (range 2 to 51). These patients under-

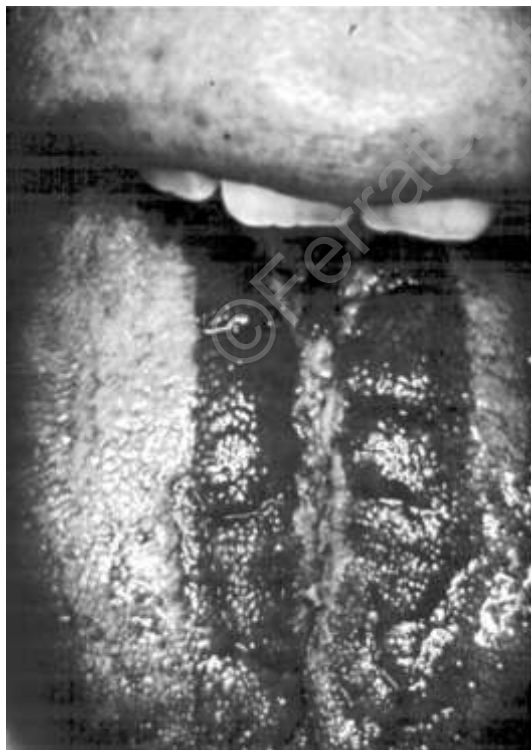


Figure 1. Erythematous candidiasis of the dorsum of the tongue.

went oral examination from 2 to 7 times. HIV-negative subjects underwent oral examination only once.

AIDS was classified according to the 1993 Revised HIV Classification System criteria.¹³ Oral examination was preceded by a standardized interview to obtain sexual, drug use, and behavioral information. The first oral examination was performed without knowing the patient's HIV status. Anatomic sites, dimensions, number, clinical aspects and symptoms of oral lesions were recorded. Details about the diagnostic criteria for HIV-related oral manifestations have been described previously.^{1,3,5} Statistical analysis was performed by means of the Mann Whitney U test.

Results

The group of 54 male hemophiliacs was composed of 36 (67%) HIV-seropositive patients and 18 (33%) HIV-negative individuals. Median age of the entire group was also 26 years (range 9 to 72 years). Median age of the HIV-positive patients was 26 years (range 10 to 72 years).

Evaluation of HIV-seropositive patient risk factors is shown in Table 1. The majority of patients suffered from hemophilia A; one patient was also bisexual and two were also intravenous drug abusers.

Analysis of patient stage revealed that half possessed a CD4⁺ T-lymphocyte count over $0.5 \times 10^9/L$ (Category 1), 10 had a count between 0.2 and $0.499 \times 10^9/L$ (Category 2) and 8 were lower than $0.2 \times 10^9/L$ (Category 3) (Table 2).

Over the course of several examinations, oral lesions were recorded in 18 (50%) out of the 36

Table 2. Clinical categories of 36 HIV-seropositive hemophiliacs.

<i>CD4 cells category</i>	#	%
1. $\geq 0.5 \times 10^9/L$	18	50
2. $0.200-0.499 \times 10^9/L$	10	28
3. $< 0.2 \times 10^9/L$	8	22
Total	36	100

Table 3. Association between clinical categories and presence of oral lesions.*

CD4 cells category	oral lesions present	
	#	%
1. $\geq 0.5 \times 10^9/L$ (n=18)	9	50
2. $0.2-0.499 \times 10^9/L$ (n=10)	8	80
3. $< 0.2 \times 10^9/L$ (n=8)	11	72**
Total (n=36)	28	

*Count refers to the total number of oral examinations.

**Statistical difference was significant ($p=0.040$)

HIV-positive patients. The percentage manifesting oral lesions increased with severity of disease (Table 3). Severity of immunosuppression and presence of oral lesions were significantly associated ($p=0.040$).

Among the 36 patients with HIV infection we observed 28 lesions of the oral cavity. No oral lesions were observed in the HIV-seronegative group. OC was the most common disturbance, followed by HL. Oral herpes simplex infection, necrotizing gingivitis and facial herpes zoster were found in a small number of patients (Table 4).

Patients with oral lesions showed a lower median CD4⁺ T lymphocyte count ($0.209 \times 10^9/L$; range 0.008 to 0.615) than those without oral lesions (median CD4⁺ count was of $0.539 \times 10^9/L$, range 0.042 to 1.180; $p=0.002$). The relationship between grade of immunosuppression and type of oral lesions among

HIV-positive patients is reported in Table 5.

OC showed different clinical forms: nine cases were atrophic, one pseudomembranous and four were not identified (Figures 1 and 2). Lesions occurred on the tongue (9 cases), palate (3), lips (2), and buccal mucosa (1). OC cultures, available in 18 patients, revealed *Candida albicans* in 17 (94%), lesions and *Candida tropicalis* in one (6%). At the diagnosis of OC, patients showed a median CD4⁺ T lymphocyte count of $0.2515 \times 10^9/L$ (range 0.008 to 0.615).

HL of the tongue was diagnosed in six patients (Figure 3). All lesions were bilateral. In one case clinical diagnosis was confirmed by histologic examination and *in situ* DNA hybridization for Epstein Barr virus (EBV); in the remaining five cases the severity of the patients coagulation defect contraindicated tissue biopsy. At the appearance of HL patients revealed a median CD4⁺ T lymphocyte count of $0.4295 \times 10^9/L$ (range 0.008 to 0.559).

Discussion

Hemophiliacs constitute one of the populations with a high prevalence of HIV positivity, which ranges from 34% to 94%.¹⁴⁻¹⁶ It is now clear that HIV infection has a long and variable latent period, determined principally by the rate of fall of CD4⁺ T lymphocyte count.¹⁷ However, other factors such as age, risk categories, individual variability in the rate of CD4⁺ T lymphocyte count fall, more aggressive HIV

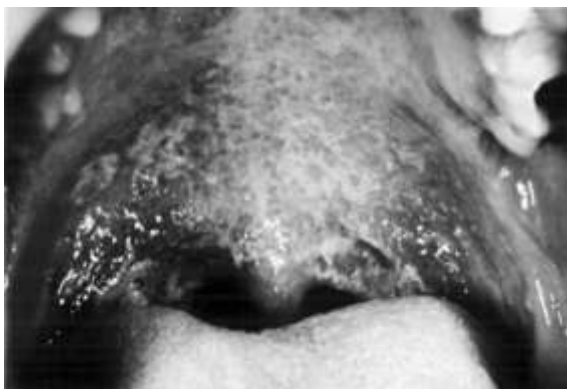


Figure 2. Pseudomembranous candidiasis of the soft palate.



Figure 3. Hairy leukoplakia of the tongue.

Table 4. Types of oral lesions among 36 HIV-infected patients.*

types	#	% of total (28 lesions)	% of total (36 patients)
Candidiasis	14	50	39
Hairy leukoplakia	6	21.5	17
Oral herpes	5	18	14
Necrotizing gingivitis	2	7	5.5
Facial herpes zoster	1	3.5	3
Total	28	100.0	

*Count refers to the total number of oral examinations

strains and antiretroviral treatment may influence prognosis and faster progression of HIV infection.¹⁸ In subjects with hemophilia the estimated rate of progression to AIDS from seroconversion to 11 years appears to be 42%.¹⁹

Our study confirmed that HIV-seropositive hemophiliacs may develop oral lesions during the clinical course of their disease. As already reported for other risk categories,^{2,3} OC and HL were among these disturbances most frequently observed. Both these lesions carry unfavorable prognostic significance,²⁰ but it is not well known whether these lesions have the same prognostic implications in HIV-seropositive hemophiliacs. Our study also shows an increased prevalence of oral lesions in subjects with lower CD4⁺ T lymphocyte counts. These findings are consistent with other reports.^{3,21} Evidence of an association between oral lesions and immune suppression may be useful as an indirect marker of CD4⁺ T lymphocyte depletion in situations where such counts are not readily available.²¹

In HIV-infected patients the loss of CD4⁺ T lymphocytes and the associated cellular immu-

nity damage facilitate the development of OC, which is often the initial manifestation of HIV infection.^{3,22} OC is the most common lesion observed in these patients and it also carries a negative predictive value for the development of AIDS.^{20,23} The clinical features of OC are extremely varied; the most common early presentation form is the erythematous type, which presents as a red area usually located on the dorsum of the tongue and palate.^{1-3, 24} In the advanced stages of HIV infection, OC is often of the pseudomembranous type and consists of white plaques that can be removed leaving an erythematous or bleeding mucosal surface.³ Angular cheilitis is another type of presentation and is often associated with a concurrent intra-oral candidal infection. Diagnosis of OC is based on clinical features, cultures from swabs, saliva and imprint cultures, oral rinse technique and tissue biopsy.^{1,3,24}

HL is considered a marker of HIV infection, although it has also been observed in HIV-negative patients suffering from other forms of immunosuppression.^{4,5,26} HL was described for the first time in HIV-infected homosexuals and

Table 5. Relationship between types of oral lesions and clinical category.

Types	#	Category 1	Category 2	Category 3
Candidiasis	14	4	4	6
Hairy leukoplakia	6	3	2	1
Oral herpes	5	-	1	4
Necrotizing gingivitis	2	1	1	-
Facial herpes zoster	1	1	-	-

subsequently in all the other HIV risk groups. It is considered highly predictive for the development of AIDS.^{4,5,27} The clinical aspects of HL are extremely variable: lesions may appear as vertical white striations, corrugations, or as flat, raised or shaggy, variably-sized plaques. They develop most often on the lateral margins and less frequently on the dorsal and ventral surfaces of the tongue or on the vestibular mucosa, soft palate, pharynx and esophagus.^{4,28,30} HL seems to be caused by replication of EBV within the epithelial cells of the tongue.^{1,4,5,25,30}

Diagnostic criteria for HL include white lesions on the lateral surfaces of the tongue that do not rub off, characteristic histologic features, and failure to respond to antifungal therapy.^{28,30} In HIV-infected patients diagnosis of HL is usually readily made on the basis of clinical aspects or a combination of clinical and histologic features. However, when HL mimics other lesions, biochemical or ultrastructural identification of the Epstein-Barr virus may be necessary to confirm diagnosis.^{28,30} In some hemophilic patients, severity of the coagulative defect may prevent tissue biopsy. In these cases alternative non-invasive diagnostic techniques such as cytology, filter and cytospin *in situ* hybridization are useful for making a definitive diagnosis of HL and identifying EBV.³¹⁻³³

In summary, we have shown that HIV-seropositive hemophiliacs may develop oral lesions during the course of HIV infection and that OC and HL are the most common manifestations. A careful oral examination should be included in the evaluation of all HIV-infected hemophiliacs.

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