

# Oral Signs Unraveling the Diagnosis of the Human Immunodeficiency Virus

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## ABSTRACT

*Human immunodeficiency virus (HIV)-related oral conditions occur in a large proportion of patients, and frequently are misdiagnosed or inadequately treated. The presence of these oral manifestations can be an early diagnostic indicator of immune deficiency and HIV-infection as well as a predictor of progression of disease. In the case presented here, the patient appeared apparently healthy and was completely unaware of his immunologic status. The progressively increasing gingival growth made him obtain a dental opinion. Eventually, the classic oral manifestations led to a revelation of his underlying immune status and the gingival growth was evaluated accordingly to arrive at a diagnosis of diffuse large B cell lymphoma. Thus, the present paper discusses the oral presentations seen in HIV and their diagnostic criteria as dental expertise is crucial for prompt diagnosis of HIV-infection and appropriate management of oral manifestations.*

**Keywords:** B-cell lymphoma, HIV, oral hairy leukoplakia

## Las Señales Orales en la Dilucidación del Diagnóstico del Virus de la Inmunodeficiencia Humana

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## RESUMEN

*Las condiciones orales relacionadas con el virus de inmunodeficiencia humana (VIH) se presentan en un gran número de pacientes, que con frecuencia son diagnosticados o tratados inadecuadamente. La presencia de estas manifestaciones orales puede ser un indicador diagnóstico temprano de deficiencia del sistema inmune e infección por VIH, así como un predictor de progresión de la enfermedad. En el caso presentado aquí, el paciente acudió aparentemente sano y con un total desconocimiento de su estado inmunológico. El crecimiento gingival cada vez mayor le hizo buscar una opinión dental. Finalmente, las manifestaciones orales clásicas condujeron a revelar su estado inmune subyacente, y el crecimiento gingival fue evaluado de conformidad con el hallazgo, con lo cual se llegó al diagnóstico de un linfoma difuso de células B grandes. El presente trabajo analiza las manifestaciones orales del VIH y sus criterios diagnósticos, ya que la experiencia estomatológica es crucial para un rápido diagnóstico de infección por VIH y el tratamiento adecuado de las manifestaciones orales.*

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## INTRODUCTION

Acquired immune deficiency syndrome (AIDS) is a disease of the human immune system caused by the human immunodeficiency virus (HIV). It has emerged as a global crisis since it came into limelight in 1981 in the United States of America. Approximately 33 million people are infected with HIV, with more than 7000 new infections reported every day (1). Undiagnosed or untreated infection with HIV results in progressive loss of immune function marked by depletion of the CD4<sup>+</sup> T lymphocytes (CD4), leading to opportunistic infections and malignancies, characteristic of the Acquired Immunodeficiency Syndrome [AIDS] (2). Oral lesions occur in 30–80% of the affected patient population and their presence directly affects patients' quality of life. The presence of oral lesions is strongly associated with a high viral load > 20 000 copies/mL, low CD4 cell count < 200 cells/mm<sup>3</sup> and treatment failure (3). These oral diseases often present with diagnostic and therapeutic hurdles, challenging the clinician to correlate with the underlying immunodeficiency. Moreover, the list of common oral manifestations may change because of the impact of modern therapy on the disease (4). Inaccurate diagnosis, lack of treatment or inappropriate treatment may result in considerable patient morbidity and potential mortality.

The focus of this case report is to discuss common HIV-associated oral pathologies and their diagnostic criteria.

## CASE REPORT

A 38-year-old male patient reported to the Department of Oral Medicine and Radiology with the main complaint of a growth on the anterior gingival region of six months duration. The patient gave a history of progressive increase in size, associated mild pain and occasional bleeding when touched. On intra-oral examination, a well-defined erythematous, exophytic growth of about 3 x 1 cm was seen on the upper left labial gingiva (Fig. 1).

It was firm in consistency and bleeding on provocation. Examination also revealed bilateral white patches on the lateral border of the tongue consistent with oral hairy leukoplakia (Fig. 2).

Soft-palate examination revealed slightly raised erythematous macules, suggestive of erythematous candidiasis (Fig. 3).



Fig. 1: Exophytic growth on the upper left labial gingival.



Fig. 2: Bilateral white patches on the lateral border of tongue consistent with oral hairy leukoplakia.



Fig. 3: Erythematous macules, suggestive of erythematous candidiasis.

Non-scrapable hyperkeratotic leukoplakic patches were noticed on the left retromolar area (Fig. 4).



Fig. 4: Hyperkeratotic leukoplakic patches on the left retromolar area.

These clinical manifestations raised a suspicion of immunodeficiency. On being questioned on social history, the patient reluctantly admitted having unprotected sexual intercourse with multiple partners. In the view of the oral signs and social history an HIV-ELISA test was carried out which returned as positive. Confirmatory tests performed for HIV were also positive and CD4 count was 292 cells/mm<sup>3</sup>. The patient was started on antiretroviral treatment. The patient was prescribed topical antifungal [clotrimazole] and topical anaesthetic agent [benzydamine hydrochloride]. Antiretroviral drugs were considered to be effective in producing regression of oral hairy leukoplakia (OHL).

Total excision of the lesion was done and sent for histopathological investigation. Histopathological examination of the sections showed diffusely arranged lymphoid cells consisting of medium to large atypical cells with irregular to round *nuclei* along with coarse to vesicular fine chromatin and eccentrically placed small nucleoli [centrocytic to centroblastic in morphology]. Presence of mitosis and an admixture of mature lymphocytes was seen (Figs. 5 and 6).

Immunohistochemistry (IHC) studies showed leukocyte common antigen (LCA)-positivity in all cells (Fig. 7). CD20-membranes were positive in sheets and CD30 were positive in reactive background population of cells (Figs. 8 and 9). The final diagnosis of diffuse large B cell lymphoma was made.

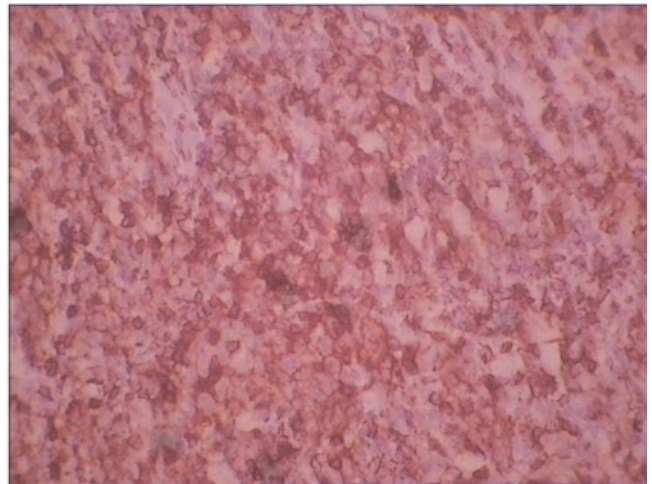
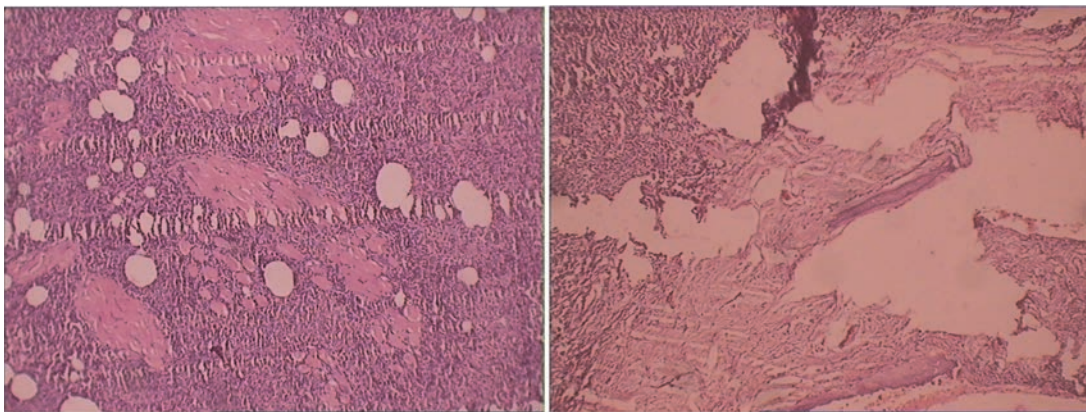


Fig. 7: Immunohistochemistry study showing leukocyte common antigen positive in all cells.



Figs. 5, 6: Diffusely arranged atypical lymphoid cells with irregular to round *nuclei*, coarse to vesicular fine chromatin and eccentrically placed small nucleoli.

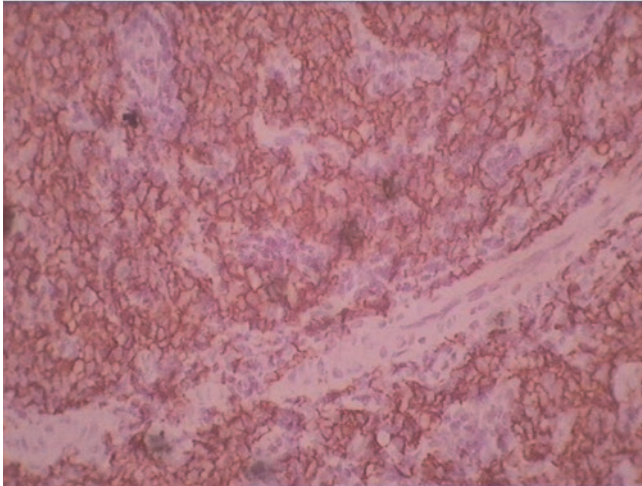


Fig. 8: Immunohistochemistry study showing CD20-membranes positive in sheets.

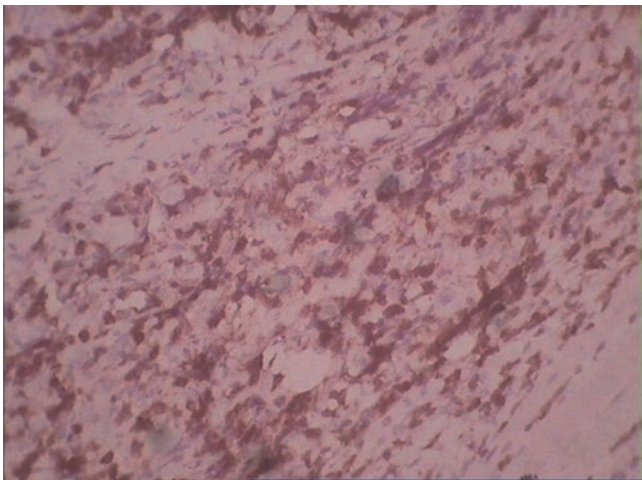


Fig. 9: Immunohistochemistry study showing CD30 positive in reactive background population of cells.

## DICUSSION

HIV-infection is characterized by progressive immunosuppression due to low absolute CD4 counts and the perturbed cytokine network which manifest *havoc* at the clinical level. Studies have shown that 70–90% of HIV-infected individuals will develop at least one oral manifestation during the course of the disease. Factors which predispose expression of oral lesions include; CD4 counts less than 200 cells/mm<sup>3</sup>, viral load greater than 3000 copies/mL, xerostomia, poor oral hygiene and smoking (5). Seven cardinal lesions: oral candidiasis, hairy leukoplakia, Kaposi sarcoma, linear gingival erythema, necrotizing ulcerative gingivitis and periodontitis and non-Hodgkins lymphoma are strongly associated with HIV-infection and have been identified internation-

ally. These lesions may be present in up to 50% of people with HIV-infection and in up to 80% of those with a diagnosis of AIDS (6).

*Oral candidiasis:* Oral candidiasis commonly presents months or years before more severe opportunistic infections in HIV patients and it may be a sentinel event indicating the presence or progression of HIV disease (5). It is typically observed as CD4 counts fall below 200 cells/mm<sup>3</sup> (4). The four common forms of presentation of *Candida albicans* infection are *pseudomembranous* candidiasis, hyperplastic candidiasis, erythematous candidiasis and angular cheilitis. *Pseudomembranous* candidiasis is the most common clinical presentation of all candidal infections [ranging from 55.8 to 69.7%], followed by erythematous candidiasis (25.7–50%), angular cheilitis (13.7–27.1%) and hyperplastic candidiasis [0–1.7%] (2). Patients may exhibit one or a combination of any of these presentations. In patients with full blown AIDS, the *pseudomembranous* form of candidiasis is most common, while in patients infected with HIV, the erythematous type is dominant (7) as seen in our case. Erythematous candidiasis appears as red areas located on the palate and dorsum of the tongue but occasionally on the buccal mucosa while *pseudomembranous* candidiasis presents as white or yellow spots or plaques located in any part of the oral cavity and can be wiped off to reveal an erythematous surface which may bleed. The definitive criteria for diagnosis is based on the response of the lesions to antifungal therapy and tests (smears or cultures) for the presence of *Candida albicans* (8). Several reports indicate that most persons with HIV-infection carry a single strain of *Candida* during clinically apparent candidiasis and when candidiasis is quiescent (9).

*Oral hairy leukoplakia (OHL):* It presents as white, non-removable vertical corrugated bands bilaterally on the lateral borders of the tongue. These lesions may appear on the ventral and dorsal surfaces of the tongue and, more rarely, on the buccal mucosa (4). It is not pathognomonic for HIV-infection since it has been described in patients who are iatrogenically immunosuppressed. There has been a marked decrease in the incidence of OHL in the potent antiretroviral era (10). Definitive diagnosis requires demonstration of Epstein-Barr virus in the lesions by laboratory histopathology and in situ DNA hybridization. If these studies cannot be performed, the lack of response to antifungal therapy may reinforce a presumptive diagnosis of OHL (8). This condition is normally asymptomatic and does not require therapy unless there are cosmetic concerns. However, it is important to note that the condition is observed with immune deteri-

oration and that patients presenting with it while on antiretroviral therapy may thus, be experiencing failure of their current regimen (10).

**Kaposi's sarcoma:** Kaposi's sarcoma is an angio-proliferative disease that may arise from a mesenchymal progenitor cell infected by human herpes virus-8. The risk of Kaposi's sarcoma in patients with HIV, which is closely associated with sexual transmission, is 5 to 10 times greater in male homosexuals than in other HIV-risk groups (11). It usually arises when the CD4<sup>+</sup> T cell count is less than 200 copies/mm<sup>3</sup> although its incidence has dramatically decreased since the advent of protease inhibitors in highly active antiretroviral therapy [HAART] (2, 11). Kaposi's sarcoma frequently involves palate, gingiva and tongue and can be macular, nodular, or raised and ulcerated, with colour ranging from red to purple. Early lesions tend to be flat, red, and asymptomatic, with the colour becoming darker as the lesion ages (4, 10). Diagnosis is frequently missed in African-American patients due to lesion coloration (4). Definitive diagnosis requires biopsy (8).

**Linear gingival erythema:** It is an unusual pattern of gingivitis appearing with a distinct linear band of erythema that involves the free gingival margin and extends 2 to 3 mm apically. In a significant percentage of cases, the alveolar and gingival mucosa may demonstrate petechiae-like patches (4). The amount of erythema is disproportionately intense for the amount of plaque seen. No ulceration or evidence of pocketing or attachment loss will be present (2). Some data indicate a relationship between sub-gingival colonization of *Candida* species and HIV-related periodontal conditions including linear gingival erythema (10). This is at present a clinical diagnosis without definitive criteria. However, a feature of the lesion is that it does not respond well to oral hygiene measures and the removal of dental plaque and calculus (8).

**Necrotizing ulcerative gingivitis (NUG):** It refers to destruction of one or more interdental papillae with no loss of periodontal attachment. In addition, interproximal gingival necrosis, bleeding, pain and characteristic fetor may be seen (4). This is a clinical diagnosis without definitive criteria (8).

**Necrotising ulcerative periodontitis (NUP):** It is characterized by gingival ulceration and necrosis associated with rapidly progressive periodontal attachment loss. This leads to severe pain, loosening of teeth, spontaneous haemorrhage, fetid odor, destruction or sequestration of bone. Patients often refer to the pain as "deep

jaw pain" (4, 10). In contrast to the typical chronic periodontitis, NUP presents as multiple isolated defects (4). This is a clinical diagnosis without definitive criteria and is now not deemed to be specific for HIV-infection.

**Non-hodgkins lymphoma [NHL]:** Non-Hodgkin's lymphoma in patients with HIV is an AIDS-defining condition (11). It is the second most common HIV-related tumour after Kaposi's sarcoma; the risk of getting NHL being 60 times greater in patients with HIV-disease than in otherwise healthy persons (12). Unlike Kaposi's sarcoma, the incidence of non-Hodgkin's lymphoma has not changed since the introduction of HAART. Presumptive diagnosis can be made based on the clinical appearance of soft-tissue masses with or without ulceration and tissue necrosis that frequently involves the gingival, palatal and alveolar mucosa, along with other oral tissues. Oral lymphoma may mimic periodontal disease, with thickening a mass, ulceration and radiographic changes, including widening of the periodontal ligament space, loss of lamina dura and bone destruction (11). Mostly, AIDS related non-Hodgkin's lymphomas are high-grade B-cell lymphomas and a rare type called plasmablastic lymphoma seems to nearly always arise exclusively in the mouth (2). Characteristic histological appearance on biopsy, supported by appropriate immunocytochemical or molecular biological investigations can lead to definitive diagnosis (8).

## CONCLUSION

A dental professional may be the first healthcare provider to encounter symptomatic disease. A meticulous oral health examination, including soft-tissue palpation of the head and neck, is important for identification of disease, especially in an unaware patient. As seen in the present case, prompt identification and referral to medical providers facilitates the team to co-manage these patients. There was significant reduction in oral lesions following three months treatment with HAART along with topical management.

With the advent of HAART, there has been a decline in overall prevalence of oral manifestations in HIV. Few studies have shown that during the HAART era, there has been a significant reduction in oral hairy leukoplakia and necrotizing ulcerative periodontitis, yet more research is needed to correlate clinical oral lesions with clinical stage of HIV disease, anti-HIV drug regimen and CD4<sup>+</sup> cell count.

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