



## THE IMPACT OF ENT COMORBIDITIES IN HIV DISEASE

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Since it appeared in the early 1980s, the acquired immune deficiency syndrome (AIDS) and the human immunodeficiency virus (HIV) that causes it have wrought physical and social devastation around the world. After many years of infection most people develop symptoms that indicate progression of the disease. There are no regular characteristic symptoms or early stage, and no logical sequence of AIDS indicator disorders has been observed. People who are not aware of the infection are referred to physicians of various specializations, including otolaryngologists which is a special issue and a perspective analysis on life in the 21st century. Over 80% of HIV-infected individuals will present with ear, nose and throat (ENT) manifestations.

The main otorhinolaryngological manifestations and their treatment were classified according to the place of the disease and the prevalence: oral manifestations, nasal manifestations, manifestations in the neck and otological manifestations.

*Keywords:* ENT, HIV, Otorhinolaryngological manifestations.

### INTRODUCTION

Retrospective studies suggest that the prevalence of head and neck symptoms is about 80%. HIV still remains a global pandemic, particularly affecting the countries of sub-Saharan Africa, Southeast Asia, and Latin America.

The increased incidence of HIV has resulted in a greater number of HIV-infected patients presenting to ENT doctors. Indeed, up to 80% of HIV-infected patients eventually develop ENT manifestations. Among the latter, oral disease seems to be the most common, occurring in approximately 40–50% of HIV positive patients. Predisposing factors for HIV-related ENT conditions include T helper cells (CD4+) cell count of less than 200/μL, plasma HIV-Ribonucleic acid (HIV-RNA) levels greater than 3000 copies/mL, xerostomia, poor oral hygiene, and smoking.

Although ENT manifestations may not be diagnostic of HIV infection, they may be heavily suggestive of such an infection. In addition, the occurrence of certain oral manifestations in patients with known HIV disease who are not receiving treatment may be related to the progression of the disease. Finally, the presence of ENT disease in patients on antiretroviral therapy could be the result of an increase in the plasma HIV-RNA and suggest treatment failure. In this context, the provision of appropriate care to HIV patients may require a multi-disciplinary approach.

The aim of the present paper is to review the current knowledge on ENT manifestations of HIV infection, and present the available diagnostic and treatment options. The implications of the early identification of HIV-associated ENT disease from a public health perspective are also discussed, along with clinical markers of immune compromise.

## MATERIALS AND METHODS

Data collection was performed by several researchers looking for cases on online platforms such as Nature, PubMed, The Lancet, Science Direct, QJM-Oxford Academic. Online databases used were in the study from 2009 to March 2021.

The main otorhinolaryngological manifestations and their treatment were classified according to the place of the disease and the prevalence. Oral manifestations: oral candidiasis; hairy leukoplakia; recurrent foot and mouth disease; neoplasms (sarcoma and Kaposi's lymphomas); conditions caused by herpes simplex, shingles and human papilloma virus (HPV); periodontal disease; and oral tuberculosis. Nasal manifestations: acute and chronic rhinosinusitis; allergic rhinitis; neoplasms (Kaposi's sarcoma and lymphomas). Manifestations in the neck: enlarged lymph nodes; involvement of the salivary gland. Otological manifestations: acute and chronic otitis media; secretory otitis media; otitis externa; polyps in the external auditory canal; neoplasm (Kaposi's sarcoma); sensory hearing loss; peripheral facial paralysis.

## RESULTS AND DISCUSSION

### ORAL LESIONS

1. Oral candidiasis, commonly known as thrush, is by far the most common oral manifestation of HIV infection. Candidal infection can occur in the oropharynx, hypopharynx, and larynx, and usually results in severe odynophagia and swallowing difficulties<sup>1,2,3</sup>. The prevalence of candidiasis varies from 30–90% among HIV positive adult patients whereas the respective percentage in children ranges between 22.5 and 83.3%<sup>3</sup>.

Oral candidiasis can present in three forms: pseudomembranous candidiasis, erythematous candidiasis, and angular cheilitis. Oral pseudomembranous candidiasis is the most common fungal infection in HIV disease. It has been associated with more frequent progression of HIV to AIDS, and also used as a clinical marker to define the severity of HIV infection. It appears as creamy, white, curd-like plaques on the buccal mucosa, tongue, and other oral mucosal surfaces. The plaques can be wiped away, leaving a red or bleeding underlying

surface. The most common organism involved is *Candida albicans*; however involvement of non-*albicans* species, such as *Candida glabrata* and *Candida dubliniensis*, has also been described<sup>1,2,3</sup>.

Erythematous candidiasis, on the other hand, presents as a red, flat, subtle lesion on the dorsal surface of the tongue, or on the hard or soft palate. The lesion often involves two opposing surfaces, if a lesion is present on the tongue, the palate should be examined for a matching lesion, *Et cetera*. Patients usually complain of a burning sensation, especially while eating spicy or salty food. When the hypopharynx, larynx, or esophagus are affected, symptoms may progress to severe odynophagia and swallowing difficulties. This may be especially true in children, in which candidal esophagitis may require hospital admission, and intravenous administration of amphotericin B. Diagnosis is based on the clinical appearance of the lesions taking into consideration the history of HIV infection. However, candidiasis can be confirmed in challenging cases from the identification of fungal hyphae or blastospores in potassium hydroxide (KOH) preparation<sup>4</sup>.

Treatment of mild to moderate cases of both erythematous and pseudomembranous candidiasis includes clotrimazole troches, nystatin oral suspension, and nystatin pastilles, whereas systemic administration of fluconazole, intraconazole and voriconazole is warranted in moderate to severe cases. Voriconazole should be reserved for cases of fluconazole resistance, due to more serious interactions with other drugs. Antifungal therapy should last for two weeks to reduce the colony forming units to the lowest level possible and prevent recurrence<sup>2</sup>.

Angular cheilitis presents as erythema, and/or fissuring in the corners of the mouth. It may co-exist with erythematous or pseudomembranous candidiasis, and persist for an extensive period of time if left untreated. Treatment involves the use of a topical antifungal cream directly applied to the affected areas four times a day for two weeks<sup>5,6</sup>.

2. Oral hairy leukoplakia is a condition almost pathognomonic of HIV infection and often indicates progression to AIDS. The lesion most frequently appears on the lateral aspect of the tongue with a thick, vertically correlated ('hairy') whitish plaque, very similar in appearance to the hyperplastic type of oral candidiasis<sup>7</sup>. Potassium hydroxide (KOH) preparations of surface scrapings will identify the

mycelia or hyphae seen in candidiasis and can therefore be used to differentiate between these two conditions. A biopsy of the lesion will be diagnostic of oral hairy leukoplakia. The Epstein-Barr virus has been identified as the most likely causative agent. Oral hairy leukoplakia is typically asymptomatic and does not usually require any treatment, but it is a significant finding because of its diagnostic and prognostic implications. The lesions have been successfully treated with aciclovir (2 g/day), sulpha drugs, zidovudine or topical retinoic acid<sup>7</sup>.

3. Kaposi's sarcoma is still the most common oral malignancy seen among patients with HIV. The prevalence of oral Kaposi's sarcoma of the mouth varies from 0-12% in Africa and 0-38% in USA and Europe. The oral cavity is commonly affected and is the first clinical site of Kaposi's sarcoma in 20% of cases, while it occurs concomitantly with skin and visceral involvement in up to 70% of patients<sup>8,9</sup>. Within the oral cavity, the hard palate is the most frequently involved, followed by the gingival and buccal mucosa, as well as the dorsum of the tongue. Kaposi's sarcoma-associated herpes virus was proven to be a co-factor in the presentation of Kaposi's sarcoma in patients with HIV. Kaposi's sarcoma can be macular, nodular, or raised and ulcerated. The color of the lesions can range from red to purple. Early lesions tend to be red, flat and asymptomatic, with the color becoming darker as the lesion ages. As lesions progress, they can become symptomatic due to trauma or infection. Biopsy of the lesion, usually under local anesthetic, is necessary for diagnosis. Following the diagnosis of Kaposi's sarcoma, oral hygiene is necessary, and topical injections of chemotherapeutic agents, such as vinblastine sulfate, or even surgical removal or radiation therapy can be considered for treatment. Several surgical techniques have been described, including cryotherapy and laser therapy. Systemic chemotherapy should be reserved for patients with both oral and extra-oral Kaposi's sarcoma<sup>8,9</sup>.

4. Non-Hodgkin's lymphoma is the second most common malignancy associated with HIV infection. Most patients present with fever, night sweats, and significant weight loss. Lymphomas associated with HIV infections may occur as single or multiple ulceration or edema lesions within the oral cavity; onset is sudden, and they usually cause no pain and grow quickly. They often develop as the first symptom of this

neoplasm<sup>10</sup>. They may be difficult to diagnose and mistaken for inflammation of mucous membranes or parodontium. Multifocal lesions have been reported in lymphomas, suggestive of ulcerations, and lesions may disappear and reappear.

The possible occurrence of multiple (concurrent or subsequent) malignancies has also been observed during recent years, after combined antiretroviral therapy became available. There has been a report of an extremely infrequent episode of nasopharyngeal actinomycosis associated with squamous adenocarcinoma occurring in a patient treated receiving combined antiretroviral therapy<sup>11,12</sup>.

5. Herpes simplex virus type 1 (HSV-1) infection is widespread and oral lesions are common. Recurrent intraoral HSV outbreaks start as a small crop of vesicles that rupture to produce small, painful ulcerations that may coalesce. Lesions on the lip are fairly easy to recognize. In the mouth, lesions on keratinized or fixed tissues, including the hard palate and gums, should prompt suspicion of HSV-1 infection. It involves reactivation of a latent virus in the trigeminal ganglion; the main form in seropositive patients is related with a fall in circulating CD4 cells and increased viral load. The CD4 cell count must be taken into account in the treatment of herpes simplex. If the count is over 200, topical treatment is used for perioral herpes simplex until the lesions clear; if the count is below 200, or if there are extensive lesions, or if the patient did not respond to topical treatment, a systemic antiviral agent such as acyclovir is warranted. Still more severe cases require endovenous medication; intravenous foscarnet may be used in patients with acyclovir-resistant strains<sup>13</sup>.

6. Lesions caused by the human papillomavirus (HPV): as with oral candidiasis, HPV lesions (papillomas, focal epithelial hyperplasia or condyloma acuminatum) are more frequent when CD4 cell counts are lower; however, as opposed to oral candidiasis and pilous leukoplakia, HPV infection rates did not decrease following antiretroviral therapy. The most common type is type 32<sup>14</sup>.

Treatment has not been well defined; acid/caustic agents, cantharidin, topical podophyllin, topical cidofovir, intralesional interferon- $\alpha$ , intralesional bleomycin, topical 5-fluoracil, or surgery (cryosurgery, Carbon dioxide (CO<sub>2</sub>) laser, curettage, or cold blade excision) may be used<sup>14</sup>.

## OTOLOGICAL MANIFESTATIONS

1. Otitis externa is caused by *Pseudomonas aeruginosa* and otomycosis is often caused by *Candida albicans*. Secretory otitis media secondary to oropharyngeal lymphoid hyperplasia is common in HIV-positive patients<sup>15</sup>. In patients with HIV infection, malignant (necrotising) external otitis has been reported. AIDS patients who develop malignant external otitis tend to be younger than the typical elderly patient with this invasive ear infection. *Aspergillus fumigatus* as well as *Pseudomonas aeruginosa* have been isolated in HIV-infected patients. Although malignant external otitis seems to be uncommon in AIDS patients, the diagnosis should be considered in any patient who presents with painful otorrhea that is unresponsive to treatment regimens for simple external otitis<sup>15</sup>.

Serous otitis media (effusion with no infection) occurs more frequently in HIV-positive adults than in the overall population. Unilateral or recurring serous otitis media requires a nasopharynx examination to exclude benign or malignant tumors of this anatomic region<sup>16</sup>. Such tumors manifest with nasal obstruction, conductive hearing impairment, acute otitis media and recurring otitis media secretoria. Diagnosis of large lymphoid proliferation of the adenoids should make the physician consider performing an HIV test and taking a detailed history concerning risk factors related to HIV infection. Adenoidectomy (resection of the adenoid) is the therapy of choice which liquidates obstructions in the eustachian tube. The material sample should be examined by a histopathologist to exclude a lymphoma and Kaposi's sarcoma<sup>15,16,17</sup>.

2. Acute otitis media is frequent in HIV patients, although etiologic factors are similar as in the general population and include *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. The management (usually antibiotic therapy) is similar to that in immunocompetent patients<sup>17</sup>.

3. Otomycosis is a chronic and superficial disease of the outer ear canal; it is generally caused by *Aspergillus niger*<sup>18</sup>. It may occur following use of antibiotics or during bacterial infection. The clinical findings are similar to those of bacterial otitis externa, but the diagnosis depends on identifying the fungus in the

histopathological exam, as *Aspergillus* is almost always a saprophyte in the outer ear canal<sup>18</sup>. The treatment consists of cleaning the outer ear canal and topical antifungal agents. If this treatment is ineffective, there may be invasive fungal infection of tissues. In this case, computed tomography or magnetic resonance imaging may be done to assess the extent of the disease. The treatment of invasive fungal infection consists of surgical debridement and systemic antifungal drugs<sup>18,19</sup>.

4. Suppurative chronic otitis media is a chronic inflammation of the middle ear and mastoid, associated with otorrhea and a perforated tympanic membrane. Bernaldez and collaborators have shown that the prevalence of this condition in seropositive children over a 10-year period was 13.24%, with a 3.31% annual incidence. The most common microorganisms in this study were *Pseudomonas aeruginosa* and *Proteus*. Therapy aims at eliminating the germs and improving patient immunity. Effective antiretroviral therapy reduces the prevalence of chronic otitis media in immunocompromised children, probably by increasing the number of CD4 T-lymphocytes<sup>20</sup>.

## SINUS AND NASAL MANIFESTATIONS RELATED TO HIV

1. Nasal obstruction and congestion are caused by a wide range of disorders, and commonly occur in HIV-positive patients. A common cause of this manifestation is adenoidal hypertrophy<sup>21</sup>. In fact, the presence of this lesion in an otherwise asymptomatic adult patient should always raise the suspicion of HIV infection. It is thought that infection with HIV, Epstein-Barr virus or cytomegalovirus causes proliferation of B cells in lymphoid adenoidal tissue. The commonly presenting symptoms are nasal obstruction and recurrent serous otitis media secondary to eustachian tube obstruction. Adenoidectomy and bilateral tympanostomy with tube placement are indicated for relief of symptoms in patients with disease refractory to medical therapy<sup>21</sup>.

2. Rhinosinusitis: this disease is very common in seropositive patients.

Paranasal sinuses are involved because of increased susceptibility to allergic rhinitis, decreased mucociliary clearance, and immune cell dysfunction. The microorganisms that cause

acute infection in the general population are the same in HIV-infected patients; the treatment, therefore is similar.

The clinical findings of acute infection are similar to those in non-HIV infected patients: headache, fever, purulent nasal discharge, nasal block, and posterior dripping. However, immunosuppressed patients are unable to mount an inflammatory response<sup>22</sup>; thus, the clinical manifestations of sinus disease in these patients may be only chronic coughing, recurring lung infection, fever of unclear origin, or central nervous system infection. Miziara and collaborators found purulent rhinorrhea, nasal block, and headache as the most common complaints in patients with chronic rhinosinusitis<sup>23</sup>. Imaging methods – computed tomography and magnetic resonance imaging are useful for the diagnosis or if there is complicated sinusitis.

The medical treatment of acute and chronic cases is similar to that in non-HIV infected patients, consisting of antibiotics against *Staphylococcus* and *Pseudomonas*. The duration of therapy is still controversial; currently, three weeks are recommended for acute cases, and four to six weeks for chronic cases. Topical or systemic decongestants may be useful.

Antibiotics based on cultures of sinus content is used in patients that do not respond to therapy, or that present toxemia or with CD4 cell counts below 50 cells/mm<sup>3</sup> at the beginning of the disease. In non-responding cases, complicated sinus disease, opportunistic infection, or neoplasms should be sought as cases of treatment failure; imaging is useful in such cases<sup>22,23</sup>.

Endoscopic surgery may be beneficial in chronic or non-responding cases to reestablish sinus drainage and to support the diagnosis for those patients.

## CONCLUSIONS

Certain conclusions are drawn regarding the manifestations of ENT in immunocompromised patients, namely:

- Routine pathogens predominate when it comes to infections of the ears, nose and throat
- HIV-positive patients should be treated initially with the same antibiotic as HIV-negative patients.
- Multiple oral lesions may be present simultaneously.

- Oral candidiasis and rhinosinusitis are the most common ENT manifestations of HIV.

- Hairy oral leukoplakia is an almost pathognomonic condition of HIV infection and often indicates progression to AIDS.

- Kaposi sarcoma is the most common oral tumor associated with HIV and occurs predominantly on the palate.

- Chronic otitis media in the adult patient should be investigated and the patient's HIV status established.

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