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HIV infections in otolaryngology

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Summary

HIV (human immunodeficiency virus) infection may produce no clinical symptoms for 10 years on average. However, 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. It is on their knowledge about HIV infections, among other factors, that early diagnosis of the disease depends. Appropriate and quick introduction of anti-retroviral drugs may let a person with HIV live decades longer.

key words: **HIV • infection • otolaryngological diseases**

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Background

A HIV-positive patient has increased risk of acquiring many diseases, ranging from the common to the very rare; this risk depends on the blood level of CD4 cells. If their number exceeds 500/mm^3, usually the patient has no clinical symptoms of the disease, which appear as the number of cells falls, and when it goes below 200/mm^3 the patient becomes susceptible to many disorders associated with HIV. As the number of CD4 cells continues to fall below 50/mm^3, the patient is at risk of acquiring multiple rare infections.

Most otolaryngologic manifestations of HIV are due to infections of variable etiology, neoplasms or primary neurologic disorders. Infections of the head and neck are usually caused by common pathogens that attack persons of normal immune defences. Rare microorganisms, pathogens related frequently with HIV infection, are usually isolated in later stages of HIV infection. HIV infection may also be associated with neoplasms of the head and neck, such as Kaposi's sarcoma and non-Hodgkin lymphomas.

Many patients with serious opportunist infections are not aware of their seropositive status. Hoffmann reports that after the year 2000, about 50% of patients diagnosed with AIDS were not previously aware of their HIV infection, and about 35% of patients had not been treated with antiretroviral drugs before the diagnosis of AIDS [1]. Persons with advanced HIV disease may not only be lacking the treatment and care they need, but are also at risk of transmitting the virus to others. It is hoped that this paper will raise awareness of certain diseases among otolaryngologists, alerting them to the real possibility that HIV infection may be an underlying concomitant illness in some patients in whom HIV testing would not previously have been considered.

Conditions Occurring in or Affecting Multiple Head and Neck Anatomic Sites

Kaposi's Sarcoma (KS)

The most common malignancy associated with HIV disease is Kaposi's sarcoma. It most commonly affects homosexual men, less frequently women, and rarely affects injection drug users. KS can manifest early in the course of HIV infection, and may be the first clinical manifestation of immunodeficiency. The typical HIV-associated KS lesion is pink or purple, not tender, and macular or slightly raised or nodular, and can occur on both cutaneous and mucosal surfaces. This process is frequently multifocal. Thus, individuals with mucosal lesions often present with easily visible cutaneous lesions as well. Clinical history and the characteristic appearance of KS often allow clinical diagnosis, which a biopsy can confirm.

The pathologic lesions within the oral cavity caused by Kaposi's sarcoma may appear earlier than those on the skin. They usually cause no complaints, unless there is a secondary infection or ulceration. In such cases, pain or bleeding may occur. Large lesions may disturb speech and eating. Lesions may be localized in any site on the oral cavity's mucous membrane, but the most frequent localization is on the palate or gums [2].

Non-Hodgkin's lymphoma (NHL)

NHL 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. 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 [3].

Lately, there has been observed a phenomenon of worldwide emergence of broad-spectrum hematological and, especially, solid organ neoplasms, which also seem to occur at a younger age and with greater aggressiveness and more frequent and more rapid mortality compared to neoplasms in the general population [4]. 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 [5].

Lesions within the oral cavity

Lesions within the oral cavity occur at a quite early stage of HIV infection. They more frequently affect persons with low level of CD4 cells, which is why their fast and correct diagnosis as a symptom of HIV infection is very important for urgent implementation of antiretroviral therapy. Many lesions within the oral cavity related to HIV infection cause intense pain [6,7].

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.

Herpes zoster, a reactivation of the varicella zoster virus (VZV), can occur along any branch of the trigeminal nerve; thus an intraoral or extraoral presentation along branches of this nerve is possible. The intraoral lesion will start as vesicles, burst and then present as oral ulcerations.

Prodromal symptoms are frequent, such as headaches, bad general disposition, and photophobia, rarely associated with fever. Cutaneous lesions are usually so characteristic that they allow for quick and correct diagnosis, but it may be more difficult in the case of untypical localizations, such as on limbs, as occurs in HIV infection, or in the case of complications. Typical cases require no further diagnostic tests. Otic zoster should be suspected in the case of sudden, unilateral loss of hearing, often difficult to notice – by the physician as well as the patient [8].

Papillomas within the oral cavity, induced by human papilloma virus (HPV), also occur in patients infected with HIV. More than 100 subtypes of HPV have been described, all of which can infect epithelial cells. At least 17 HPV DNA types have been detected in oral mucosal lesions, the more common of which include subtypes 2, 6, 11, 13, 32 and 57 [9]. Oral warts may appear cauliflower-like, spiked, or raised with flat surface. The incidence of human warts due to HPV has increased in the potent antiretroviral therapy era. Reznik reported that the risk of HPV-associated oral warts is associated with a 1 $\log_{10}$ or greater decrease in plasma HIV RNA level within the 6 months prior to oral HPV diagnosis, suggesting that the development of warts may be related to immune reconstitution [10].

Epstein-Barr virus (EBV) may cause the following symptoms in HIV-positive patients: thickening of epithelial cells of the tongue or, less frequently, other parts of the oral cavity, referred to as oral hairy leucoplakia. Such lesions were observed for the first time in 1984 in homosexual men [11]. They are slightly less frequent in women, and they sporadically affect children infected with HIV. Hairy leucoplakia develops also in other forms of immunosuppression, such as in transplant recipients or after chronic corticoid therapy. It is very rare in immunocompetent persons. Oral hairy leucoplakia presents as a white, corrugated lesion on the lateral borders of the tongue; the lesion cannot be wiped away. 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 deterioration and that patients presenting while on antiretroviral therapy may thus be experiencing failure of their current regimen [10].

Yeasts of the Candida type are a component of the natural bacterial flora of the human oral cavity, present in 20% to 50% of adults. Developing impairment of the immunology system related to HIV infection predisposes to yeast colonization in the oral cavity, as documented at the onset of the AIDS epidemic [11]. Diagnosis of candidiasis of the oral cavity in a previously asymptomatic patient suggests increased replication of the virus and progression of the infection [13]. Oral candidiasis has several clinical forms. The most frequent form is pseudomembranous candidiasis, presenting as white stains of 1–2 mm diameter, occasionally bigger, on the mucous membrane of the oral cavity. They are single or multiple and may coalesce; they can be removed, but leave a reddened or even bleeding surface of the mucous membrane [12]. Hyperplastic candidiasis is a rarer form, also referred to as candidal leukoplakia, that often causes pain. Erythematous candidiasis may be the most underdiagnosed and misdiagnosed oral manifestation of HIV infection. The condition presents as a red, flat, subtle lesion on the dorsal surface of the tongue or on the hard or soft palate. It may present as a "kissing" lesion; if a lesion is present on the tongue, the palate should be examined for a matching lesion, and vice versa. The condition tends to be symptomatic, with patients complaining of oral burning sensation, most frequently while eating salty or spicy foods or drinking acidic beverages. Clinical diagnosis is based on appearance, as well as on the patient's medical history and virologic status. Angular cheilitis presents as erythema or fissuring of the corners of the mouth. It can occur with or without oral candidiasis, and can persist for an extensive period of time if left untreated [10,11].

Oral candidiasis is often associated with taste impairment and a feeling of burning. Confirmation of oral candidiasis is a clinical diagnosis based on the characteristic appearance of the lesions. Recurring candidiasis or bad reaction to treatment falls into the B category of clinical stages of HIV infection as categorized by the U. S. Centers for Disease Control and Prevention [14].

The presence of hairy leukoplakia and/or pseudomembranous candidiasis indicates progression to AIDS [15].

With the advent of highly effective antiretroviral therapy, the prevalence of oral candidiasis, oral hairy leukoplakia, and Kaposi's sarcoma has decreased in adults [10,15].

Nose and Sinuses

Nasal complications of HIV infection and AIDS are very common. Cutaneous lesions may be caused by Kaposi's sarcoma, herpes virus infections, seborrhea-like dermatitis and herpes zoster. Some of them may be the first symptom of advanced, symptomatic HIV infection.

Patients with immunodeficiency due to HIV infection may suffer from giant herpetic ulcers, which commonly originate in the nasal vestibule and can extend to involve the nasolabial region. The lesion can be diagnosed by history and clinical appearance, and the diagnosis can be confirmed by culture or Tzanck smear.

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 [16]. 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.

Chronic sinusitis is frequent in patients with immune deficiency caused by HIV, with an incidence of up to 60% in some series [17], acute or chronic, with or without mucopurulent postnasal drainage. Causative organisms include atypical opportunistic organisms, such as *Alternaria alternata*, *Aspergillus sp.*, *Pseudoallescheria boydii*, *Cryptococcus neoformans* and *Candida albicans*, as well as agents responsible for sinusitis in hosts without HIV infection. Just as in seronegative hosts, HIV-positive patients with sinusitis have signs and symptoms of fever, general and localized headaches, and mucopurulent drainage from sinus ostia. Plain sinus radiographs should be performed to confirm the diagnosis [19]. In some cases fever and/or headaches are the only symptoms; therefore sinusitis needs to be considered in the differential diagnosis of unexplained fever or headache, especially in individuals with low CD4 cell counts. Maxillary involvement appears to be the most common site in individuals with HIV, followed by ethmoidal sinusitis. Often both of these sinuses are involved at the same time. Frontal and sphenoidal sinusitis occur less frequently [19]. The severity

of sinusitis in HIV-positive patients correlates directly with the level of CD4 count. In these patients tomographic methods are preferable to conventional radiology [20].

Although depressed cellular immunity results in decreased total lymphocyte and CD4 counts, polyclonal B-cell activation produces increased circulating immune complexes with increased production of IgA, IgG, and IgE. This excessive IgE production is associated with increased IgE-mediated allergic symptoms, including allergic rhinitis. Sample et al. [21] reported a 2-fold increase in the incidence of allergic symptoms in HIV-infected men after HIV infection. The presentation can include perennial profuse thick rhinorrhea and nasal congestion [22].

Jütte et al. [23] described a case of CMV sinusitis leading to diagnosis of HIV infection and CMV retinitis, stressing that diseases of the sinonasal tract may represent an initial manifestation of HIV or even AIDS. Meanwhile, Boumis, et al. [24] presented a case of rhino-orbital zygomycosis secondary to diabetic ketoacidosis in an HIV-positive patient. Probably induced by the HIV protease inhibitors the patient had been taking, diabetic ketoacidosis was a predisposing condition to this infection. Thus, patients treated with antiretroviral medications, especially HIV protease inhibitors, are at risk of ketoacidosis and may therefore develop zygomycosis.

Sinusitis poses a difficult clinical challenge in HIV-infected patients because of high rates of relapse and association with unusual pathogens. If the sinus disease or its complications persist despite extensive medical therapy, surgery should be considered. Endoscopic sinus surgery (ESS) was successful in providing marked alleviation of symptoms associated with chronic sinusitis and nasal disease in HIV-infected persons, and patients reported significant subjective improvement in nasal obstruction. Friedman et al. [25] reported that patients undergoing standard ESS have a satisfactory success rate; HIV-infected patients with surgical indication for ESS should be treated as non-HIV-infected patients, and low CD4 count ($<100/mm^3$) does not serve as a contraindication for definitive surgery.

Ears

The otological manifestations associated with HIV include seborrheic dermatitis of the external ear, otitis externa with otomycosis, secretory otitis media, sensory neural hearing loss, and vertigo [26].

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 [22].

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 [27]. *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 [22].

Serous otitis media (effusion with no infection) occurs more frequently in HIV-positive adults than in the overall population [26]. Unilateral or recurring serous otitis media requires a nasopharynx examination to exclude benign or malignant tumors of this anatomic region. 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.

Acute otitis media is frequent in HIV patients, although etiologic factors are similar as in the general population and include *Streptococcus pneumoniae, Hemophilus influenzae* and *Moraxella catarrhalis*. The management (usually antibiotic therapy) is similar to that in immunocompetent patients [28].

Otitis media and mastoiditis caused by *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) is a rare opportunist infection that almost exclusively affects HIV-positive patients. An aural polyp is frequently found in the external auditory canal or middle ear that on biopsy reveals typical *P. jiroveci* cysts if stained with Grocott-Gomori methenamine silver nitrate [28].

Hearing loss may be common among HIV-infected people, as cross-sectional studies and case reports show. Most of these patients have had sensorineural hearing loss that steadily worsened with increasing frequencies, becoming moderate at high frequencies, but speech discrimination was usually near normal. A possible etiology is a primary infection by HIV of either the central nervous system or peripheral auditory nerve. Clinicians should consider other causes of sensorineural hearing loss in HIV-infected patients, such as central nervous system infections, neoplasms, and past medications, particularly ototoxic agents. Aural rehabilitation with hearing aids should be considered for HIV-infected patients with no identified cause of hearing loss [22].

Practical Results

It is important that physicians recognize the earliest signs and symptoms of HIV infection in order that timely diagnosis and patient referral can be made for early counseling, testing, and treatment. In patients diagnosed earlier, the disease may have slower progression because of the restorative effect of combination antiretroviral therapy on immune function.

Conflict of interest

The authors declare there is no conflict of interest. The corresponding author affirms that there are no relations with any company whose products are mentioned in the paper or with any company that distributes competitive products. The presentation of the subject is independent and the content of the paper is neutral toward all products.

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