Human immunodeficiency virus infection: personal experience in changes in head and neck manifestations due to recent antiretroviral therapies

La modificación de las manifestaciones de la infección por el VIH: un enfoque personal

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Both the incidence and prevalence of human immunodeficiency virus infection are increasing in the world. Diseases of ENT districts are more frequent in patients infected with the human immunodeficiency virus, and involve all the otorhinolaryngological sites. The otorhinolaryngological manifestations in association with HIV infection are mainly atypical, so common in the clinical practice, really aspecific and very frequent in ENT daily routine (such as sinusitis, otitis, etc.) and, therefore, immunodeficiency may not be suspected. In other cases, ENT evidence is more peculiar or unusual, such as opportunistic infections, rare neoplasms and tumours with an unusual course, giving a very high suspect of a human immunodeficiency virus-related infection. The most frequent malignant neoplasm is Kaposi’s Sarcoma which is extremely rare in non-human immunodeficiency virus-infected subjects; the second most frequent is non-Hodgkin’s lymphoma with 50% in extranodal sites (oral and maxillary sinus). Following a review of the literature, modifications caused by current antiretroviral treatment on head and neck manifestations of human immunodeficiency virus infection have been evaluated. Highly active antiretroviral therapy is a new therapeutic strategy, based on poly-chemo-therapeutic schemes, providing simultaneously two or more anti-retroviral drugs. We have used highly active antiretroviral therapy in human immunodeficiency virus infection since 1997, substituting previous mono-chemotherapy based on Zidovudine or Didanosine alone. Highly active antiretroviral therapy is extremely efficient in reducing the viral load of human immunodeficiency virus and increasing CD4+ T-lymphocyte count. These biological effects are associated with an improvement in immune functions. To evaluate the effects of highly active antiretroviral therapy on otorhinolaryngological manifestations in human immunodeficiency virus infection, we performed a retrospective study on 470 adults, observed over 14 years (1989-2002) and constantly receiving the same treatment, with follow-up from 7 to 80 months. A total of 250 subjects underwent mono-antiretroviral chemotherapy (1989-1996), while 220 underwent highly active antiretroviral therapy (1997-2002). The results of the retrospective study showed that highly active antiretroviral therapy has greatly improved the control of the immune-deficiency (increasing the range of CD4+), reducing the
number of otorhinolaryngological manifestations (also tumours). On the other hand, 2 patients presented sudden unilateral hearing loss following treatment: toxicity due to association of new drugs cannot be excluded.

Introduction

Ear, Nose and Throat (ENT) diseases in patients with human immunodeficiency virus (HIV) infection are numerous and involve all the otorhinolaryngological sites. Since ENT manifestations are frequently the earliest symptoms of immunodeficiency, before HIV infection has been detected, the real challenge is not the ENT diagnosis, but the ability to suspect HIV infection as a cause.

In most cases, the ENT clinical outcomes are not specific for HIV infection and are so common in clinical practice (for example, sinusitis, otitis, etc) that immunodeficiency may not be suspected.

In other cases, ENT evidence is more peculiar or unusual. It is thus essential to recognise them since the suspicion of HIV-related infection is very high.

Epidemiology of ENT manifestations in HIV infection

The incidence and prevalence of HIV infection are both increasing in the world. The increasing trend in paediatric infections, with high peaks being reported in the poorer areas, has given rise to some anxiety. For example, a study performed in Cambogia on 50,000 children and 23,000 adults revealed a high prevalence of HIV seropositivity with no significant differences being observed between children (3.6%) and adults (5.4%).

Disorders in ENT districts are more frequent in HIV-infected patients, as the upper airways are the natural interface between the organism and the environment. Head and neck diseases present mainly through atypical manifestations, and, therefore, the acquired syndrome is not suspected as the determining factor, thus leading to negative diagnostic and prognostic consequences.

ENT disorders, already common in childhood, are more and more frequent in HIV-infected children. Some geographically distant studies (India and Great Britain) have shown that otorhinolaryngological symptoms are the presenting symptoms in at least 50% of children with HIV. Moreover, 55% of the HIV children presented their first ENT disease before 3 years of age and 98% before age 9. Since ENT disorders are often the initial presentation of the HIV infection in children, serum assays for HIV-infection are increasingly recommended.

The median age at diagnosis of patients with head and neck manifestations was 33 years, with a male to female ratio of 3:1.

As far as concerns transmission, a study performed in Italy on HIV patients with ENT involvement revealed an equal distribution between drug transmission (50%) and sexual transmission (50%), with 36% homosexuals and 14% heterosexuals.

In children, transmission is primarily perinatal and vertical (mother-to-child). A study performed in London revealed an increasing incidence of paediatric HIV infection, and reported that the maternal country of origin was Africa in 70% and that transmission was vertical in 90%.

OPPORTUNISTIC HEAD AND NECK INFECTIONS AND MALIGNANT TUMOURS

Infection from HIV is well known for the progressive, particular host susceptibility to a variety of opportunistic infections and malignant neoplasms. The frequency of bacterial opportunistic infections in HIV patients is increasing, including infections caused by Pseudomonas Species. Since the range of ear, nose and throat manifestations caused by Pseudomonas aeruginosa is very broad, clinical suspicion is necessary, combined with accurate microbiological data, in the treatment of these potentially life-threatening infections. Furthermore, treatment using combination chemotherapy, such as ciprofloxacin and ceftazidime, is advisable, as it has been shown that dual therapy results in a significantly lower mortality.

Cases of opportunistic protozoa infection have been reported in the literature, such as mucocutaneous leishmaniasis involving the nasal, pharyngeal and laryngeal districts. Carbonell et al. described only one case of laryngeal leishmaniasis which was the onset of AIDS in a patient not known to be HIV+. In particular, these authors stressed that laryngeal leishmaniasis had not previously been described as the onset of AIDS.

HIV patients are at greater risk of developing cancer. Although no tumour has been shown to develop exclusively in association with HIV infection, malignancies in these patients present a different clinical behaviour, response to treatment and prognosis from that observed in HIV negative hosts.

The most frequent malignant neoplasm is Kaposi’s sarcoma (KS), being extremely rare in non-HIV-infected subjects. The second most frequent neoplasm is Non-Hodgkin’s lymphoma (NHL). KS and NHL are tumours that alone are diagnostic of AIDS in patients with HIV infection.

The majority of HIV-infected patients with KS and NHL have ENT localizations, perhaps because lymphatic tissue, which is a HIV target, is well represent-
ed in this area and contamination by infectious agents (such as Epstein-Barr virus and cytomegalovirus, probably involved in the pathogenesis of KS and NHL) can easily occur in the head and neck 9.

The incidence of KS has increased together with the epidemic spread of AIDS all over the world 12. A study carried out in Italy, in 1992 10, revealed an incidence of 6.6% as far as concerns the localization of KS in the head and neck (14/210 HIV positive patients underwent ENT examination without symptom-related selection). All patients were male, with a median age of 40 years, 11/14 were homosexual. The concomitant involvement of skin and mucosa was the common manifestation and the palate was the most frequently affected mucosal site.

Epistaxis, nasal obstruction, sore throat, dry or foreign body feeling in the throat and nodal mass are the most frequent manifestations 12.

Only 50% of NHL of the neck, in association with HIV infection, are located in the cervical nodes. The other 50% are found in an extranodal site (oral and maxillary sinus).

As a result, not only may NHL be considered as onset evidence of HIV infection, but, in the case of extranodal location, HIV infection must always be suspected and detected 11.

Barzan et al. 10 found a prevalence of 11% (14/210) of head and neck NHL localisations in HIV patients. An extranodal site was the most frequent characteristic, while the gums were the site most commonly involved.

An increased incidence of skin tumours, squamous cell carcinomas 13 and Hodgkin’s lymphomas (HL) have also been observed, but not yet confirmed by epidemiological data, which, so far, have not recorded any increase in head-neck carcinomas despite HIV epidemic diffusion.

Albeit, it is important to recall that the main problem raised by these tumours is the confounding infection which may lead to late diagnosis or an error in tumour staging 14.

**OTHER HIV-RELATED HEAD AND NECK MANIFESTATIONS**

Unlike the opportunistic infections, rare neoplasms (KS) and tumours with an unusual course (NHL), the other ENT manifestations, in association with HIV infection, are really aspecific and are very frequent in daily ENT routine. Those disorders are the most insidious and challenge our ability to suspect unknown HIV infections.

In adults, the most frequent head and neck diseases are:

- oropharyngeal candidiasis: 22-57% 4 15 16;
- chronic rhinosinusitis: 11-27% 4 16;
- cervical lymphadenopathies.

Oropharyngeal candidiasis is a frequent disease, but when diagnosed in a young patient not treated with radio-, chemo- or immunosuppressive therapy, HIV infection should certainly be suspected.

Cervical lymphadenopathy of unknown origin is also a very common problem in everyday practice: HIV infection must always be considered as a possible cause. Many other otolaryngological HIV-related manifestations have been reported in adults. These may be outlined, according to the different sites, as follows:

**Ear**

- chronic and recurrent otitis media 3;
- hearing loss mainly of conductive origin caused by otitis media and tubal stenosis 3;
- sudden hearing loss 17;
- vestibular loss.

**Nose and paranasal sinuses**

- mucociliary changes due to rhinitis and hypertrophy of the nasal mucosa 3 18;
- nasal vestibulitis 3;
- epistaxis 3;
- nasal septum perforation as onset presentation 19;
- mixed hyposmia and hypogeusia due to involvement of multiple cranial nerves 3.

**Neck**

- neck swellings which mimic branchial cysts 20;
- benign lymphoepithelial parotid cysts 21;
- tubercular retropharyngeal abscess (case report with no other tubercular locations in AIDS) 22.

**Oral cavity and pharynx**

- Herpes Simplex 15;
- Non-malignant nasopharyngeal lymphoid hypertrophy 23.

In children, where lymphatic diseases of tonsils, adenoids and middle ear, cervical nodes are very common themselves, the suspicion of HIV infection is often a great challenge.

The most frequent manifestations are 16:

- cervical lymphadenopathies (40-70%);
- oropharyngeal candidiasis (35-60%);
- adenotonsillar diseases (30-40%);
- otitis media (18-46%);
- diffuse parotid swelling (5%).

**History of antiretroviral drugs**

AZT (Zidovudine, Retrovir) was the first anti-retroviral drug, being available since 1987. Since 1991, DDI (Didanosine, Videx) has also been available. Both drugs belong to the so-called “nucleoside reverse transcriptase inhibitors” (NRTI) and, at first, were used alone (mono-therapy). Since 1994, they have also been combined.
The turning point for anti-retroviral therapy is 1996 when "protease inhibitors" (PI) were introduced. These drugs, displaying comparable toxicity, are much more potent and are employed combined with the NRTI. HAART is a combination of nucleoside reverse transcriptase inhibitors and protease inhibitors. This new therapeutic strategy is highly efficient in reducing the HIV viral load and increasing CD4+ T-lymphocyte count. These biological effects are associated with an improvement in immune functions.

A third category of drugs has been introduced in 1996, the "non-nucleoside reverse transcriptase inhibitors" (NNRTI), these also associated with the others. The antiretroviral drugs currently used are outlined in Table I.

### Table I. Antiretroviral drugs.

<table>
<thead>
<tr>
<th>Class</th>
<th>Brand name</th>
<th>Generic name (Abbreviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside Reverse Transcriptase Inhibitors (NRTI)</td>
<td>Retrovir</td>
<td>Zidovudine (AZT)</td>
</tr>
<tr>
<td></td>
<td>Videx</td>
<td>Didanosine (DDI)</td>
</tr>
<tr>
<td></td>
<td>Hivid</td>
<td>Dideoxycytidine (DDC)</td>
</tr>
<tr>
<td></td>
<td>Zerit</td>
<td>Stavudine (d4T)</td>
</tr>
<tr>
<td></td>
<td>Epivir</td>
<td>Lamivudine (3TC)</td>
</tr>
<tr>
<td></td>
<td>Ziagen</td>
<td>Abacavir (ABC)</td>
</tr>
<tr>
<td></td>
<td>Viread</td>
<td>Tenofovir (TDF)</td>
</tr>
<tr>
<td>Protease Inhibitors (PI)</td>
<td>Agenerase</td>
<td>Amprenavir (APV)</td>
</tr>
<tr>
<td></td>
<td>Crixivan</td>
<td>Indinavir (IDV)</td>
</tr>
<tr>
<td></td>
<td>Norvir</td>
<td>Ritonavir (RTV)</td>
</tr>
<tr>
<td></td>
<td>Kaletra</td>
<td>Lopinavir/ritonavir (LPV/r)</td>
</tr>
<tr>
<td></td>
<td>Viracept</td>
<td>Nelfinavir (NFV)</td>
</tr>
<tr>
<td></td>
<td>Fortovase</td>
<td>Saquinavir (SQVsgc)</td>
</tr>
<tr>
<td>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)</td>
<td>Viramune</td>
<td>Nevirapine (NVP)</td>
</tr>
<tr>
<td></td>
<td>Sustiva</td>
<td>Efavirenz (EFV)</td>
</tr>
</tbody>
</table>

### Table II. Classification into two groups of the subjects according to the therapy.

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>250</td>
<td>220</td>
</tr>
<tr>
<td>Male</td>
<td>70%</td>
<td>75%</td>
</tr>
<tr>
<td>Female</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>26-64</td>
<td>29-68</td>
</tr>
<tr>
<td>Therapy</td>
<td>Mono-therapy</td>
<td>HAART</td>
</tr>
<tr>
<td>(AZT or DDI)</td>
<td>52 on 2 NRTIs</td>
<td>168 2 NRTIs +</td>
</tr>
<tr>
<td></td>
<td>1 IP/NNRTI</td>
<td></td>
</tr>
<tr>
<td>CD4+ lymphocytes*</td>
<td>12-350</td>
<td>150-750</td>
</tr>
</tbody>
</table>

*CD4+ lymphocytes (at time of ENT manifestations).

### Changes in Head and Neck Diseases Due to Recent Anti-Retrovirus Therapies: Personal Experience

In the literature, no studies have been performed yet on the relations between ENT manifestations and current therapeutic approach, with the exception of the recent Brazilian study, which is focused on the main HIV-related oral infections. The report compares two groups of HIV patients treated with double vs triple therapy (with a protease inhibitor) and stresses the significant decrease observed in the incidence of oral infections in the group receiving triple therapy.

We then aimed to perform a study including all the ENT manifestations observed in our personal experience.

Since 1997, we have adopted poly-chemo-therapeutic schemes, simultaneously providing two or more anti-retroviral drugs, according to the principles of the HAART.

To evaluate HAART effects on ENT manifestations, we carried out a retrospective study on 470 adults, followed over the last 14 years (1989-2002) and continuously on the same therapy with a follow-up of 7...
to 80 months (subjects with follow-up <6 months were excluded). These 470 patients have been classified into two groups according to treatment (Table II). Results are outlined in Table III.

The following conclusions have emerged from these data:

- HAART has greatly improved the control of immuno-deficiency (CD4+ ranging from 12-350 in group 1 to 150-750 in group 2);
- meanwhile, ENT manifestations were reduced by 2/3, namely from 79% in group 1 to 27% in group 2;
- the incidence of tumours is clearly reduced (from 3% to 0);
- oropharyngeal candidiasis is drastically decreased in frequency;
- no benign lymphoepithelial parotid cysts are observed in group 2 (HAART);
- two cases were observed of sudden unilateral hearing loss, a pathological association already reported in the literature 17. However, due to the small number of cases, the hypothesis of an occasional association cannot be excluded. Moreover, as these cases belong exclusively to group 2, toxicity due to new drug associations could also be taken into consideration.

<table>
<thead>
<tr>
<th>Head and neck diseases in HIV patients</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumours</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic KS with oral involvement</td>
<td>5/250 (2%)</td>
<td>0/220</td>
</tr>
<tr>
<td>NHL (maxillary sinus)</td>
<td>1/250</td>
<td>0/220</td>
</tr>
<tr>
<td>Pharynx carcinoma</td>
<td>1/250</td>
<td>0/220</td>
</tr>
<tr>
<td>Total tumours</td>
<td>7/250 (3%)</td>
<td>0/220 (0%)</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal candidiasis</td>
<td>115/250 (46%)</td>
<td>22/220 (10%)</td>
</tr>
<tr>
<td>Acute viral/bacterial pharyngitis</td>
<td>45/250 (18%)</td>
<td>25/220 (11%)</td>
</tr>
<tr>
<td>Acute/chronic sinusitis</td>
<td>14/250 (6%)</td>
<td>6/220 (3%)</td>
</tr>
<tr>
<td>Acute/chronic otitis media</td>
<td>12/250 (5%)</td>
<td>4/220 (2%)</td>
</tr>
<tr>
<td>Total infections</td>
<td>186/250 (75%)</td>
<td>57/220 (26%)</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign lymphoepithelial parotid cysts</td>
<td>3/250 (1%)</td>
<td>0/220 (0%)</td>
</tr>
<tr>
<td>Sudden hearing loss</td>
<td>0/250 (0%)</td>
<td>2/220 (1%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>196/250 (79%)</td>
<td>59/220 (27%)</td>
</tr>
</tbody>
</table>

References


