ORIGINAL PAPER

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

La modificazione delle manifestazioni dell'infezione da HIV a carico dei distretti testa-collo in conseguenza delle recenti terapie antiretrovirali: esperienze personali

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Key words

HIV • AIDS • ENT manifestations • Antiretroviral therapy

Parole chiave

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Summary

Both the incidence and prevalence of human immunodeficiency virus infection are increasing in the world. Diseases of ENT districts are more frequent in human immunodeficiency virus-infected patients and involve all the otolaryngological 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 neoplasm 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

Riassunto

Sia l'incidenza che la prevalenza dell'infezione da HIV nel mondo stanno aumentando. Le manifestazioni ORL nei pazienti con infezione da HIV sono numerose e coinvolgono tutti i distretti. Spesso si tratta di manifestazioni non specifiche, con quadri patologici talmente comuni nella pratica clinica (sinusiti, otiti, etc.) da rendere improbabile il sospetto clinico di infezione da HIV. Altre volte le manifestazioni sono più particolari e inusuali, tali da fornire un sospetto molto alto di infezione da HIV: fra esse ricorderemo le infezioni opportunistiche, le neoplasie rare come ad esempio il sarcoma di Kaposi (KS), estremamente raro nei soggetti non infetti, o i tumori dal decorso clinico inusuale quali il Linfoma Non-Hodgkin (NHL) a localizzazione extranodale (cavo orale e seno mascellare). Dopo avere fatto una revisione della letteratura sulle manifestazioni della malattia da HIV a livello dei distretti ORL, abbiamo valutato le modificazioni di tali manifestazioni indotte dalle innovazioni riguardanti le terapie antiretrovirali. L'HAART (highly active antiretroviral therapy) è una nuova strategia terapeutica, basata su uno schema di poli-chemioterapia che prevede la somministrazione contemporanea di due o tre farmaci antiretrovirali, altamente efficace nel ridurre la carica virale dell'HIV e nell'aumentare il numero dei linfociti T CD4+. Per valutare gli effetti dell'HAART sulle manifestazioni ORL dell'infezione da HIV abbiamo effettuato uno studio retrospettivo su 470 pazienti, seguiti in un periodo di 14 anni (1989-2002), sottoposti ad una terapia continua e immodificata con un follow-up da 7 a 80 mesi. Di questi pazienti 250 vennero sottoposti negli anni dal 1989 al 1996 a mono-terapia antiretrovirale, mentre i 220 trattati dal 1997 al 2002 furono sottoposti ad HAART. Il risultato dello studio retrospettivo ha dimostrato che l'HAART ha migliorato notevolmente il controllo della immunodepressione (aumentando il range dei CD4+), riducendo contemporaneamente il numero delle manifestazioni ORL correlate, anche tumorali. Come possibile effetto avverso della terapia, segnaliamo la comparsa in due casi, al termine della terapia, di una ipoacusia improvvisa monolaterale: una tossicità correlata alle nuove associazioni farmacologiche non può pertanto essere esclusa.

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 otolaryngological 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 [1], 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%) [2].
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 [3].
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 otolaryngological symptoms are the presenting symptoms in at least 50% of children with HIV [4 5]. Moreover, 55% of the HIV children presented their first ENT disease before 3 years of age and 98% before age 9 [5]. Since ENT disorders are often the initial presentation of the HIV infection in children, serum assays for HIV-infection are increasingly recommended [1].
The median age at diagnosis of patients with head and neck manifestations was 33 years, with a male to female ratio of 3:1 [4].
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 [3].
In children, transmission is primarily perinatal and vertical (mother-to-child) [4 6]. 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% [5].

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 [7].
Cases of opportunistic protozoa infection have been reported in the literature, such as mucocutaneous leishmaniasis involving the nasal, pharyngeal and laryngeal districts [8 9]. Carbonell et al. [9] 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 [10].
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) [10 11]. 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 [10].
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 lymphoadenopathies.

Rhinosinusitis is very common and, therefore, HIV infection may not be suspected. Furthermore, it is important to bear in mind HIV infection when oral candidiasis or cervical lymphoadenopathies are diagnosed.
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 [1 6]:
– 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 date 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.

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

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

	Group 1	Group 2
Period	1989-1996	1997-2002
Cases	250	220
Male	70%	75%
Female	30%	25%
Age (years)	26-64	29-68
Therapy	Mono-therapy (AZT or DDI)	HAART 52 on 2 NTRIs 168 2 NRTIs + 1 IP/NNRTI
CD4+ lymphocytes*	12-350	150-750

Abbreviations: see text.
*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 [24], 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

Table III. Results of retrospective study on 470 adults observed over 14-year period (1989-2002) and under same continuous treatment with follow-up from 7 to 80 months (subjects with follow-up < 6 months were excluded).

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

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.

References

[1] Hadfield PJ, Birchall MA, Novelli V, Bailey CM. *The ENT manifestations of HIV infection in children*. Clin Otolaryngol 1996;21:30-6.

[2] Bogomil'skii MR, Rumiantsev AG, Iakushenkova AP, Sabo O. *ENT lesions in children with AIDS*. Vestn Otorinolaringol 2002;1:4-6.

[3] Zambetti G, Luce M, Ciofalo A, Leonardi M, Filiaci F. *Otorhinolaryngological aspects of HIV infections: personal experience*. Allergol Immunopathol 1994;22:192-6.

[4] Deb T, Singh NB, Devi HP, Sanasam JC. *Head and neck manifestations of HIV infection: a preliminary study*. J Indian Med Assoc 2003;101:93-5.

[5] Singh A, Georgalas C, Patel N, Papesh M. *ENT presentations in children with HIV infection*. Clin Otolaryngol 2003;28:240-3.

[6] Chaloryoo S, Choypitayasunondh T, Chiengmai PN. *AIDS in ENT in children*. Int J Pediatr Othorinolaryngol 1998;44:103-7.

[7] Hern JD, Ghufoor K, Jayaraj SM, Frosh A, Mochloulis G. *ENT manifestations of Pseudomonas Aeruginosa infection in HIV and AIDS*. Int J Clin Pract 1998;52:141-4.

[8] Grasa JM, Lorente J, Crego F, Naches S, Subirana FX, Calderon JR, et al. *Nasal leishmaniasis in an HIV-positive patient*. Acta Otorrinolaringol Esp 2000;51:169-73.

[9] Carbonell Casasus J, Cnovas Llorens DL, Soler Villarrasa R, Mas MS. *Leishmaniasis and ENT*. An Otorrinolaringol Ibero Am 1995;22:139-49.

[10] Barzan L, Tavio M, Tirelli U, Comoretto R. *The cervicofacial manifestations of Kaposi's sarcoma and of Hodgkin's lymphomas in HIV-infected patients*. Acta Otorhinolaryngol Ital 1992;12:107-17.

[11] Zapater E, Bagan JV, Campos A, Armengot M, Abril V, Basterra J. *Non-Hodgkin's lymphoma of the head and neck in association with HIV infection*. Ann Otolaryngol Chir Cervicofac 1996;113:69-72.

[12] Zhang R, Huang X, Tan C. *Kaposi's sarcoma associated with HIV in otorhinolaryngology. Report of 21 cases*. Lin Chuang Er Bi Yan Hou Ke Za Zhi 1997;11:64-5.

[13] Barry B, Gehanno P. *Squamous cell carcinoma of the ENT organs in the course of HIV infection*. Ann Otolaryngol Chir Cervicofac 1999;116:149-53.

[14] Peyrade F, Taillan B, Lebrun C, Dujardin P. *Cancer in pa-*

tients infected with the human immunodeficiency virus. The unusual aspects. Presse Med 1999;28:809-14.

15 Riederer A, Bujia J, Vogel T, Wilmes E, Kastenbauer E. *Otorhinolaryngologic manifestations in patients infected by acquired immunodeficiency virus*. Acta Otorrinolaringol Esp 1990;41:277-80.

16 Sacko HB, Ag Mohamed A, Maiga MY, Kalle A, Doumbia SY, Guindo A. *ORL manifestations observed in AIDS. Apropos of 65 cases*. Bull Soc Pathol Exot 1995;88:234-5.

17 Solanellas Soler J, Soldado Patino L, Lozano De Leon F. *Sudden hearing loss and HIV infection*. Acta Otorrinolaringol Esp 1996;47:311-3.

18 Armengot M, Climent B, Carda C, Ortega E, Basterra J. *Clinical and ultrastructural evaluation of nasal mucociliary function in HIV-positive patients. Preliminary investigation*. Acta Otorrinolaringol Esp 1997;48:27-30.

19 Rejali SD, Simo R, Saeed AM, de Carpentier J. *Acquired immune deficiency syndrome (AIDS) presenting as nasal septal perforation*. Rhinology 1999;37:93-5.

20 Whitworth IH, Birchall MA, Stafford ND. *Neck swelling which mimic branchial cysts in HIV-positive patients*. Ann R Coll Surg Engl 1993;75:417-21.

21 Riederer A, Bujia J, Zietz C, Vogel T, Wilmes E, Kastenbauer E. *Benign lymphoepithelial parotid cysts in patients infected with the human immunodeficiency virus*. Acta Otorrinolaringol Iberico Am 1991;18:157-68.

22 Melchor Diaz MA, Domingo Carrasco C, Monge Jodra R, Marino Esuelas J, Ontanon Martin M. *Tuberculous retropharyngeal abscess in an HIV patient: Report of a case*. Acta Otorrinolaringol Esp 1993;44:467-70.

23 Hickey SA, Buckley JG, Macartney JC. *Adenoidal hypertrophy as the presenting feature of HIV infection*. J Laryngol Otol 1990;104:58-60.

24 Miziara ID, Valentini M, Romano FR, Miniti A. *Changing patterns of buccal manifestations in AIDS*. Rev Laryngol Otol Rhinol 2002;123:231-4.

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