Multiple AIDS-related malignancies just in the era of potent antiretroviral therapy. A rare but intriguing finding

Neoplasie plurime AIDS-correlate insorte nell’era delle potenti terapie antiretrovirali. Un rilievo insolito, ma di particolare interesse epidemiologico e patogenetico

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INTRODUCTION

Kaposi’s sarcoma, non-Hodgkin’s lymphoma, primary central nervous system lymphoma and invasive cervical cancer are still the only neoplastic diseases associated with the definition of full-blown AIDS according to the 1993 revised CDC classification system [1], since their frequency is much higher than that of other neoplasms observed among HIV-infected patients [1, 2]. However, multiple different neoplastic disorders have been reported since the early AIDS pandemic (including Hodgkin’s lymphoma, anal carcinoma, oropharyngeal, esophageal and gastric carcinoma, lung cancer, multiple myeloma, testicular and ovarian neoplasms, melanoma, skin cancer, thyroid cancer, leiomyosarcomas, angiosarcomas, smooth muscle tumours, brain cancer, and others), and their overall frequency seems to have slowly increased in recent years [3-10] despite the introduction of HAART, which became the standard for antiviral treatment of HIV disease in the year 1996. Of 735 patients with AIDS notified by our reference centre in northern Italy since 1985, 70 (9.5%) were diagnosed on the grounds of an AIDS-defining cancer, while 53 more patients (7.2%) developed a malignancy when suffering from AIDS. However, to our knowledge no cases of dual AIDS-associated neoplastic disease were reported until the year 2000.

A surprisingly rare combination of invariably lethal Kaposi’s sarcoma and non-Hodgkin’s lymphoma was observed in two patients who came to our attention recently, at the height of the HAART era.

CASE REPORTS

Two homo-bisexual male patients aged 44 and 36 years respectively, with HIV infection detected 9 and 11 years before death, received multiple antiretroviral treatment lines from 1992 and 1990, respectively: monotherapy and dual therapy with nucleoside analogue reverse transcriptase inhibitors alone, followed by triple combinations based on protease inhibitors, and subsequently multiple therapeutic regimens containing non-nucleoside reverse transcriptase inhibitors, with or without one or two protease inhibitors. Notwithstanding these therapeutic attempts, the virological response remained transient and incomplete in both the presented cases, since complete viral suppression (plasma HIV-RNA levels <50-400 copies/mL, according to the different laboratory techniques used through time) was achieved by the second patient and maintained for only six months, while peak values of viremia of 270,000 and 230,000 HIV-RNA copies/mL respectively, were reached during the last five-year follow-up. Concurrently, the
A degree of HIV-related immunodeficiency remained appreciable, as expressed by a CD4+ lymphocyte count ranging from 67 to 355 cells/µL in the first patient, and between 38 and 223 cells/µL in the second case, during the last five years of clinical and laboratory monitoring. A first AIDS-associated neoplasm was identified five years before death in the first subject (a diffuse skin Kaposi’s sarcoma with associated esophageal-gastric localization was diagnosed), and two years before lethal outcome in our second patient (it was represented by a disseminated cutaneous and mucous Kaposi’s sarcoma). Administration of repeated antineoplastic chemotherapy cycles based on adriblastine, bleomycin and vincristine, and subsequent treatment with liposomal daunorubicin, attained a slowly progression of neoplastic disease, while a number of HIV-related opportunistic infections became apparent during the subsequent months and years: multi-metameric herpes zoster, recurrent pneumonia, associated with wasting syndrome in the first subject, and esophageal candidiasis and cryptosporidiosis in the second observed patient. In both our patients the CD4+ lymphocyte count remained persistently below 200 cells/µL, after detection of Kaposi’s sarcoma. Five and eleven months respectively before their lethal outcome, our patients suffered from a high-grade non-Hodgkin’s lymphoma discovered by biopsy of multiple enlarged axillary lymph nodes, and confirmed also at mediastinal, pleural and pulmonary sites (while bone marrow was unaffected by the neoplastic disease) in the first case, while a highly malignant Burkitt’s B-cell lymphoma affecting multiple skin sites and scalp (Figure 1), and borne by bone marrow, and gastro-duodenal, gingivo-buccal, and multiple pulmonary localizations was diagnosed in the second patient. In the latter case, initial, atypical multiple skin lesions (Figure 1) were the clue for diagnosis, as obtained by cutaneous biopsy. Notwithstanding multiple therapeutic attempts (high-dose zidovudine plus methotrexate as first-line chemotherapy, followed by repeated attempts with MNCOP-B regimens plus human granulocyte-colony stimulating factors), this last neoplastic disorder had a rapidly fatal course, and represented the first cause of death in both our patients, as demonstrated by combined clinical and necropsy studies.

**DISCUSSION**

The introduction of HAART has led to a profound change in the natural history of HIV disease since 1996, especially after a sharp drop of frequency of the vast majority of opportunistic disorders related to a severe HIV-related immunodeficiency as expressed by a low CD4+ lymphocyte count [9-12]. Prolonged patients’ survival, the persistence of important functional alterations of immune system response (extended to the cytokine and cell network responsible for the control of neoplastic diseases), and continuing infection with potentially oncogenic viruses, may represent the pathogenetic background responsible for a slowly proportional increase in the incidence of neoplastic disease (both haematological and solid tumours) among HIV-infected patients also during the HAART era [3, 5-10]. However, when comparing different surveys this observation was not uniform, especially for Kaposi’s sarcoma [12, 13], probably due to the favourable effects of antiretroviral and anti-herpetic medications on the possible causative agents of this malignancy.
As described by a number of cohort studies, as well as small series and anecdotal reports [3, 5, 6, 8-10], this phenomenon seems to extend beyond the classical AIDS-defining neoplasms [1, 2, 5, 8], since other neoplastic illnesses have been described with a proportionally increased incidence, compared with that of the general population, and that of HIV-infected patients followed before the introduction of HAART into daily clinical practice [2, 6, 9, 10]. Unfortunately, since notification remains restricted to neoplastic disorders included in the 1993 revised AIDS classification system [1], and cancer occurring after other AIDS-defining diseases is not reported in epidemiological surveys and surveillance programmes, these clinical manifestations may be largely underestimated in both official surveys and the international scientific literature.

However, judging from data in the international literature the occurrence of a dual AIDS-associated neoplastic disease remains an extremely rare event: to the best of our knowledge, only two patients with a rare and aggressive primary effusion non-Hodgkin’s lymphoma of null-cell phenotype and prior Kaposi’s sarcoma have been described to date by Ascoli and coworkers [14]. Although our patients developed two “classical” AIDS-defining neoplasms (Kaposi’s sarcoma first, followed by non-Hodgkin’s lymphoma), this phenomenon may become of increasing concern in the near future, and may involve more rare cancer diseases. Moreover, multiple skin localizations of non-Hodgkin’s lymphoma have an atypical presentation (Figure 1), and only skin biopsy and histopathological examination allowed us to reach a timely diagnosis. From a pathogenetic point of view, the considerable increase in life expectancy of patients treated with HAART, the persisting of supporting immunopathologic conditions, and possibly a direct involvement of HIV itself, might represent major causes of increasing frequency and a broadening spectrum of life-threatening neoplastic complications even in patients taking HAART. Moreover, some cancers associated with HIV infection may be driven by oncogenic viruses, including Epstein-Barr virus (EBV), Herpes Simplex virus type 8 (HSV-8), Cytomegalovirus (CMV), Papillomavirus, and possibly other viral agents [7, 8], thus explaining the tendency to develop more frequent neoplastic complication in the long-term course of HIV disease. In our preliminary experience, persistent HIV-associated immunodeficiency characterized by a limited recovery of CD4+ cell count, and an incomplete virological response to HAART (two conditions shared by both reported patients), might contribute to this phenomenon.

Health-care providers caring for HIV-infected patients should pay careful attention to this increasing incidence of neoplastic disease, and should maintain high clinical vigilance for a broad spectrum of cancer in all individuals with HIV disease, even after a first diagnosis of AIDS-related neoplastic illness. Epidemiological studies should better focus this phenomenon, in order to give a reliable estimate of the frequency of all neoplasms in the setting of HIV disease, and recognize the possible occurrence of dual AIDS-associated tumours. Finally, pathogenetic mechanisms underlying AIDS-related cancer deserve more insight on the grounds of neoplasm immunity and viral oncogenesis.

Key words: Dual cancer, HIV disease, highly active antiretroviral therapy (HAART), epidemiology.

SUMMARY

Two exceedingly rare cases of dual AIDS-associated neoplasms (Kaposi’s sarcoma and non-Hodgkin’s lymphoma), occurring in a short time as AIDS-defining diseases of two HIV-infected patients treated with highly active antiretroviral therapy (HAART) are reported and discussed in light of evidence from the available literature. A slowly progressive increase in neoplastic complications following the introduction of HAART and the consequent decline of opportunistic infections such as the main AIDS-related disorders has been observed, and combined cancer diseases may be expected in the next few years, due to the persistent dysregulation of the immune system, or a possible involvement of oncoviruses and HIV itself in the pathogenesis of HIV-associated cancer.
Presentiamo due casi estremamente rari di duplici neoplasie AIDS-correlate (sarcoma di Kaposi e linfoma non-Hodgkin), occorsi in un breve arco di tempo quali patologie di malattia conclamata in due pazienti con infezione da HIV trattati con highly active antiretroviral therapy (HAART). La nostra osservazione viene discussa sulla base delle più recenti evidenze di letteratura disponibili al riguardo. Un lento, ma progressivo incremento della frequenza delle complicazioni neoplastiche a seguito dell’introduzione dell’HAART come terapia standard dell’infezione da HIV, ed il parallelo declino delle patologie infettive opportunistiche nell’ambito dell’ampio spettro di affezioni definenti l’AIDS conclamata sembrano concretizzarsi negli anni più recenti, al punto che anche associazioni di diverse patologie tumorali possono divenire un evento atteso nel medio-lungo termine, a causa della permanente disregolazione del sistema immunitario e del possibile coinvolgimento patogenetico ad opera dello stesso virus HIV o di altri virus a potenziale oncogeno.

**REFERENCES**


