

ORIGINAL RESEARCH

Lung cancer in patients with HIV infection: is it AIDS-related?

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HIV-infected individuals have an increased risk of malignancy, especially non-Hodgkin's lymphoma and Kaposi's sarcoma. Recently, several workers have noted a raised prevalence of lung cancer in HIV-positive subjects. We describe the diagnosis and clinical course for four HIV-seropositive patients who presented with lung cancer. All of the patients were young and were heavy smokers. They were all on highly active antiretroviral therapy (HAART), although the adherence varied from poor to excellent. The CD4 cell counts of these patients ranged from 200 to 686 cells/ μ L and their viral loads ranged from undetectable to 29 000 HIV-1 RNA copies/mL. After initial diagnosis of HIV infection between 5 and 13 years previously, they all presented with advanced lung cancer, with a very short clinical course, and all four died within 2–9 months of diagnosis. A comparison of the incidence of lung cancer in patients with HIV infection at our centre with that in the general population suggests that there is an increased prevalence in the HIV-infected patients. We review the literature and discuss whether lung cancer in HIV infection is coincidental or related to the primary disease.

Keywords: HAART, HIV, lung cancer, non-AIDS-defining tumours

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Introduction

HIV-infected individuals have an increased risk of malignancy, especially non-Hodgkin's lymphoma and Kaposi's sarcoma [1]. Recently, several workers have noted a raised prevalence of lung cancer in HIV-positive subjects [1–3]. We describe the diagnosis and clinical course of four HIV-seropositive patients who presented with lung cancer.

Report

Cases

Case 1 was a 39-year-old single male smoker (25 pack-years) who was first discovered to have HIV infection 13 years previously. He subsequently developed Hodgkin's disease (HD), and achieved complete remission after chemotherapy with cyclophosphamide, hydroxydoxorubicin (adriamycin), oncovin[®] (vincristine), prednisone (CHOP).

Although he was prescribed HAART, he exhibited poor adherence to therapy. He presented with a persistent cough and weight loss. A chest X-ray demonstrated a mass in the lower lobe of the right lung, and this finding was confirmed by computed tomography. A pleural puncture revealed an exudate with malignant cells. A thorascopic biopsy of the mass disclosed an anaplastic giant cell carcinoma of the lung (Fig. 1). Treatment was instituted with gemcitabine to no avail, and the patient died 4 months later from tumour progression leading to respiratory failure.

Cases 2–4 are described briefly, together with a summary of case 1, in Table 1. All were relatively young men (average age 42 years) and heavy smokers. They were all on HAART, although adherence varied from fair to excellent. The CD4 cell counts of these patients ranged from 280 to 686 cells/ μ L and their viral loads ranged from undetectable to 28 000 HIV-1 RNA copies/mL. They all presented with advanced lung cancer and died within 2–9 months of diagnosis.

Incidence of lung cancer in HIV-positive patients

The incidence rate of lung cancer in these four male patients over a 10-year period (January 1999 to December

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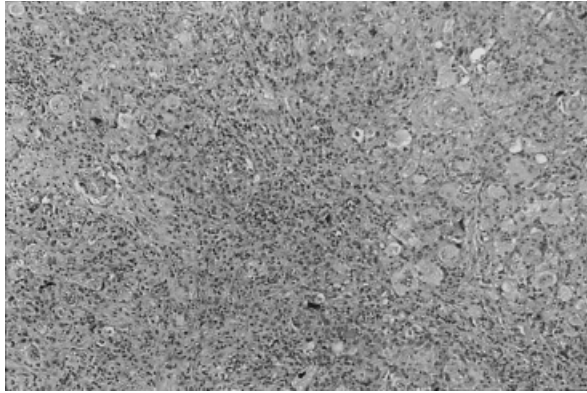


Fig. 1 Giant cell anaplastic carcinoma with numerous multinucleated malignant cells [haematoxylin and eosin (H&E), $\times 20$].

2002) was 4 per 270 patients, approximately 1.5 per 1000 patients per year. Although not significantly different, this incidence was 10 times that of lung cancer in the general population in the same age group, which is 15 per 100 000 per year, according to the Israeli Tumor Registry. The median age for the incidence of lung cancer in this registry is 65–69 years.

As all four patients were smokers, we compared the incidence rate with that for the same age group in an American Cancer Society study [4], where lung cancer mortality was 24 deaths/100 000 persons, this figure being only about 1/6 the incidence in our patients.

Discussion

We describe diagnoses and clinical courses for four HIV-seropositive patients who presented with different histological types of carcinoma of the lung: anaplastic giant cell, squamous cell (Fig. 2) and adenocarcinoma (Fig. 3). All of the patients were less than 50 years old and were heavy smokers. They received HAART, but adherence varied from poor to excellent. The CD4 cell counts and viral loads of these patients were variable. Prior to the appearance of lung cancer, their course was fairly long, with a range between 5 and 13 years (mean of 10 years). However, in all cases, after presentation with lung cancer, the clinical course was very short and they died within 2–9 months of diagnosis.

Certain epidemiological patterns are emerging with respect to lung cancer in HIV-positive patients. The pulmonary neoplasm usually occurs at a much earlier age than in the general population [5–7], the patients are invariably smokers [6,7] and the predominant histological type in most, but not all, series is adenocarcinoma [5,6,8]. As in our cases, most patients present at a late stage [5],

Table 1 Clinical features and courses for four HIV-positive patients with carcinoma of the lung

Patient	Sex	Age (years)	Risk group	Cigarette smoking (pack-years)	Time from HIV diagnosis (years)	HAART compliance	CD4 count (cells/ μ L)	Viral load (copies/mL)	Previous AIDS-defining disease	Clinical features	Histology	TNM classification	Treatment	Survival in months	Cause of death
1	M	39	B	25	13	Poor	200	29 000	HD	Weight loss, cough, mass in RLL	Anaplastic giant cell carcinoma	T3N2M0	Gemcitabine	4	Tumour progression, respiratory failure
2	M	39	B	40	8	Incomplete	467	87	Headache, cerebral mass, mass in LLL	Squamous cell carcinoma	T3N0M1	Irradiation of brain, lung lobectomy	2	Pneumonia (mixed): MAI, <i>Pneumococcus</i> , <i>Aspergillus</i>	
3	M	42	B	40	5	Good	280	28 000	Chest pain, dyspnoea, infiltrate in LLL, hepatic metastases	Squamous cell carcinoma	T3N0M1	Gemcitabine cis-platinum	4	Tumour progression, respiratory failure	
4	M	49	MSM	20	13	Good	686	< LLD	MAI	Haemoptysis	T3N2M1	Vinorelbine	9	Tumour progression	

HD, Hodgkin's disease; MAI, *Mycobacterium avium* intracellulare; RLL, lower lobe of right lung; LLL, lower lobe of left lung; LLD, lower level of detection; B, bisexual; MSM, men having sex with men.

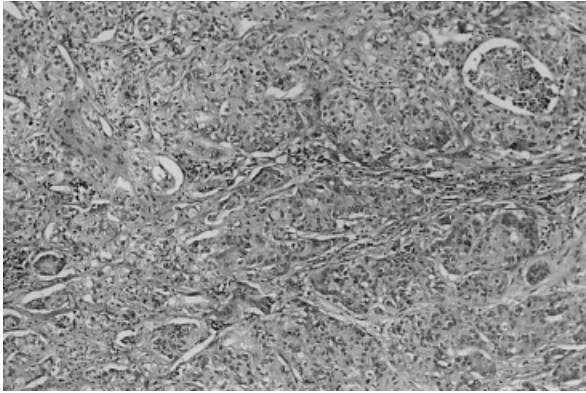


Fig. 2 Moderately differentiated squamous cell carcinoma associated with slight lymphoid infiltrate (H&E, $\times 20$).

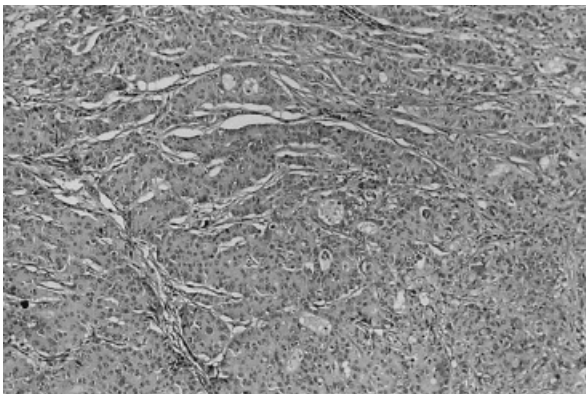


Fig. 3 Epidermoid cells in sheet-like arrays with areas of adenocarcinoma differentiation; mucus demonstrated in the lumen. (H&E, $\times 20$).

with inoperable disease and a short survival time [6], the median being 3–5 months, as opposed to 9–10 months for non-HIV-infected patients with lung cancer [8–11].

A major source of controversy is whether the presence of lung cancer in patients with HIV infection is a coincidence or is in fact related to the primary disease. Most varieties of immune deficiency typically have an increased risk of malignancy [12–14]. Certain AIDS-defining malignancies that occur at the lowest CD4 levels have exhibited the greatest decline in incidence since the onset of HAART, lending indirect support to a role for immunosuppression in tumour development [15]. Kaposi's sarcoma, non-Hodgkin's lymphoma (NHL) and cervical cancer are considered to be AIDS-defining neoplasms. They occur at a much higher incidence in patients with AIDS and also in post-transplant subjects than in other individuals. These immune deficiency-related cancers are generally associated with a viral cause, such as human herpes virus (HHV)-8 for

Kaposi's sarcoma, Epstein–Barr virus (EBV) for NHL, and human papillomavirus (HPV) for cancer of the cervix. However, of interest is the finding that post-heart transplant patients have a 25-fold higher prevalence rate of lung cancer than the general population [16], and that most of these subjects are smokers. Kidney transplant subjects also exhibit increased risk ratios for lung and other cancers as compared to the general population [17].

As the AIDS epidemic has continued, the spectrum of non-AIDS defining neoplasms has expanded [6]. Until 1990, the occurrence of lung cancer in HIV-positive patients was considered coincidental [18]. In 1990, a 14-fold increase in the risk of lung cancer was described in HIV-positive patients [19]. Subsequently, epidemiological studies demonstrated conflicting results. In an Italian AIDS cohort study, a significantly increased (18-fold) risk of lung cancer was found [20]. In another series, HIV-seropositive patients had a 6.5-fold increase in the incidence of lung cancer compared to non-HIV-infected subjects [21]. In a very large population of patients with AIDS in the USA, the prevalence of lung cancer was increased 4.5-fold [22]. Most patients with lung cancer in HIV infection are male. However, a study of 1300 women, most of whom were smokers, found that HIV-infected women were twice as likely to develop lung cancer as uninfected women [23]. In a study in Southern Europe, an excess of lung cancer was observed among intravenous drug users but not among homosexual men [24].

Nevertheless, considerable controversy exists with respect to the increased incidence of lung cancer in AIDS. A working group from the International Agency for Research in Cancer evaluated the carcinogenic risks in HIV infection and failed to find an increase in the incidence of lung cancer [25]. A community-based study demonstrated an increased overall incidence of cancer in HIV-infected subjects, but not of lung cancer [26]. In South Africa, there was no increased incidence of most non-AIDS-defining neoplasms, including lung cancer [27]. A large Australian study found an increased incidence of certain cancers but not of lung cancer [28].

In HIV-positive subjects, where tumours are apparently not virally related, the pathogenesis is unclear. Proposed mechanisms for lung cancer in HIV infection include a general impairment of cellular immune surveillance [29], additional local immune suppression caused by cigarette smoking [30] and genomic instability [31]. Although research is still at a preliminary level, a retrovirus-induced animal model for pulmonary adenocarcinoma may support the possibility of a viral aetiology for human adenocarcinoma [32].

A further question relates to the effect of HAART on the natural history of tumours in HIV-infected patients. Since

the introduction of HAART, the incidence of the AIDS-defining tumours, Kaposi's sarcoma and NHL, has decreased [15,33,34]. However, a recent study suggests that the incidence of lung cancer may be rising in the HAART era [35]. The true incidence of primary lung cancer in HIV-infected persons and the factors involved should be investigated in further studies [36].

Conclusion

As the AIDS epidemic proceeds, the spectrum of tumours has increased to include non-AIDS-defining neoplasms. Although lung cancer is not a predominant tumour in patients with HIV infection, evidence is accumulating that it too may be an AIDS-associated condition. Several workers have demonstrated an increased incidence of lung cancer in HIV-positive subjects, and this finding is to some extent supported by the cases presented here. It is possible that HAART skews the incidence curve of lung cancer to the right, as a result of prolonged survival and suppression of viral-associated tumours and other opportunistic infections. Physicians should educate their patients to avoid smoking because they are already at an increased risk of cardiovascular disease, and possibly also at an increased risk of lung cancer.

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