Aerodigestive cancers in HIV infection

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Purpose of review

Aerodigestive (lung, head and neck) cancers are among the most prevalent and deadly neoplasms worldwide, and the incidence rates are rising. Given the improvements in life expectancy of persons with HIV/AIDS when treated with highly active antiretroviral agents, persons with HIV infection are therefore increasingly likely to develop these malignancies. This chapter focuses on the epidemiology of these malignancies and reviews the most recent literature and current understanding of the causes and treatment of these malignancies in HIV-positive populations.

Recent findings

Aerodigestive neoplasms in patients with HIV infection are associated with younger age at diagnosis, cigarette smoking, advanced stage at presentation, and a more aggressive clinical course. The causes of these cancers, aside from the traditional risk factors of tobacco and alcohol exposure, are not clear. Although these neoplasms are non–AIDS defining, factors that might contribute to risk include HIV-related immunosuppression and co-infection with high-risk human papillomavirus subtypes.

Summary

With continued improvements in therapies for HIV, the expected increase in incidence and mortality of persons with HIV infection from aerodigestive malignancies will likely become a major public health concern. Given the younger age of HIV-infected patients with these malignancies and the apparently higher rates of smoking among HIV-positive individuals, aggressive smoking cessation efforts should be directed to this high-risk population.

Keywords

acquired immunodeficiency syndrome, head and neck cancer, human immunodeficiency virus, human papillomavirus, lung cancer

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Abbreviations

HAART	highly active antiretroviral therapy
HPV	human papillomavirus
SCCHN	squamous cell carcinoma of the head and neck

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Introduction

Individuals infected with HIV are known to have an increased risk of malignancy, especially non-Hodgkin's lymphoma, Kaposi's sarcoma, and invasive cervical cancer. All three of these cancers are AIDS defining; however, the proportion of deaths of persons with AIDS from non–AIDS-defining malignancies seems to be increasing [1]. Although both non-Hodgkin's lymphoma and Kaposi's sarcoma can have significant manifestations within the upper aerodigestive tract (including lymphadenopathy and mucosal manifestations), several workers have noted that primary carcinomas of the lung and head and neck have a raised prevalence in HIV-positive subjects [2••,3]. In adults with HIV infection, lung cancer is the second leading cause of cancer-related death, behind non-Hodgkin's lymphoma [4••]. The causes of aerodigestive malignancies aside from known risk factors such as tobacco and alcohol exposure are not clear, and recent publications have speculated as to whether the increased risk of these diseases in HIV-infected populations is coincidental or related to the primary disease [5,6].

Lung cancer

Lung cancer remains the most prevalent cancer and the leading cause of cancer death for both men and women in the United States. In 2005, the estimated number of new cases of lung cancer is 173,000, and approximately 164,000 individuals will die of this disease [7]. Although the incidence of lung cancer in the United States has declined among men, only recently has there been a stabilization of rates among women after a continual increase for several decades. Decreasing lung cancer incidence and mortality rates reflect decreased smoking rates over the past 30 years.

Large epidemiologic studies

Among HIV-infected individuals, however, the rates of lung cancer are higher, and incidence rates seem to be increasing. In a study by Herida *et al.* [8] that compared the incidence of non–AIDS-defining cancers in a large French HIV-infected population (77 025 patients) before highly active antiretroviral therapy (HAART) was available (1992–1995) with the incidence in the post-HAART era (1996 and beyond), only Hodgkin's disease and lung cancer were found to have a significantly higher incidence for both sexes in the post-HAART era. There was no significant difference, however, in the pre-HAART incidence rate of lung cancer in HIV-infected patients compared with the French general population. The explanation for the rates of lung cancer was attributed to the improved survival of HIV-infected patients receiving HAART and to decreased competitive mortality risks.

Frisch *et al.* [3] linked United States population-based AIDS (302834 patients) and cancer registry data to examine the general cancer pattern among adults with HIV/AIDS. Lung cancer was the most frequently observed non–AIDS-defining malignancy, and all histologic subtypes were represented (including small cell carcinomas, adenocarcinomas, and squamous cell carcinomas). Several non–AIDS-defining cancers were seen in excess, including cancers of the lung, lip, salivary gland, oral cavity and pharynx, larynx, and esophagus; however, both lung cancer and lip cancer met predefined statistical criteria to suggest possible influence by immunosuppression. For lung cancer, the relative risk increased from 1.2 in the distant pre-AIDS period to 2.7 in the recent pre-AIDS period and 2.8 in the early post-AIDS period (P for trend <0.001).

Clifford *et al.* [2••], in a retrospective analysis of the large Swiss HIV Cohort Study (7304 patients), found a threefold excess risk of cancers of the trachea, lung, and bronchus in all persons infected with HIV. No cancers from these sites were observed in nonsmokers, and excess risks were insensitive to CD4 counts. There was no significant difference in risk between HAART users and nonusers.

Case–control studies

Although large epidemiologic studies have given valuable information on the incidence of lung cancer in HIV-infected individuals, much of what we know about the treatment of these patients and their prognosis has come from small case–control studies and case series. Demopoulos *et al.* [9] compared the results in 57 cases of HIV-positive patients with malignancies at Bellevue Hospital from 1993 to 1997 with the results in 519 HIV-negative control patients. Patients with cancers of the lung, larynx, tongue, and skin (nonmelanocytic) were found to be significantly younger than those in the control group. A larger proportion of patients with HIV had a history of smoking ($P = 0.04$) or a history of illicit drug use ($P < 0.001$) compared with the control patients, but there was no difference in the two groups ($P = 0.17$) in the proportion of patients reporting a history of alcohol use.

Case–control studies of patients in the pre-HAART era suggested a more aggressive clinical course of lung cancer in patients with HIV. Tirelli *et al.* [10] examined the presentation and outcome in 36 Italian patients with HIV and lung cancer diagnosed from 1986 to 1998, in comparison with 102 control patients. The median CD4 count was 150/mm^3; only 3 patients had HAART exposure. Patients with lung carcinoma and HIV infection were younger and had previously smoked more cigarettes per day than the control group. Although all tumor subtypes of non–small cell carcinoma and small cell carcinoma were seen, the main histologic subtype was adenocarcinoma, seen in both case and control groups. Although tumor stage was similar in the two groups (mostly stages III and IV), the median overall survival was significantly shorter in patients with HIV than in the control group (5 months compared with 10 months, $P = 0.0001$). Only 3 of 9 patients with early-stage (stage I–IIIA) disease were treated with curative-intent surgery. Vyzula and Remick [11] examined the records of 16 patients with HIV infection and lung cancer diagnosed from 1988 to 1995 in New York. Compared with an HIV-indeterminate group of patients with lung cancer, patients with HIV infection and lung cancer presented at an earlier age of diagnosis and had a significantly worse survival. As many as 50% of patients had asymptomatic to mildly symptomatic HIV infection, with a median CD4 count of 184/μl. Alshafie *et al.* [12] found in 11 HIV-seropositive patients with lung cancer in New York City from 1990 to 1994 that lung cancer was diagnosed at an earlier age and had poorer outcome than in an HIV-indeterminate control group.

A case–control study specifically for patients with lung cancer in the post-HAART era was recently published [13]. Nine patients with HIV-related non–small cell lung cancer were identified after 1996 (post-HAART era). For each HIV-positive patient, 3 HIV-negative control individuals were identified and matched for age, gender, and stage of disease. The HIV-positive patients and HIV-negative control individuals had similar characteristics in terms of percent with stage IV disease (approximately two thirds of patients; the remainder had stage IIIB disease) and proportion with adenocarcinoma (approximately two thirds of patients; the remainder of HIV patients had squamous cell carcinomas); however, HIV-positive patients seemed to have a worse performance status at presentation (78% of HIV-positive patients had significant symptomatic disease as opposed to 48% of HIV-negative patients). Of the patients with HIV infection, 3 patients had no detectable HIV viremia, and 4 had received diagnoses of an AIDS-defining illness before the development of lung cancer. The median survival in both patient groups was similar at 4 months. The two groups received a similar number of chemotherapy cycles, and stable disease or partial response was achieved in 50% of treated patients in both groups. There were no chemotherapy-related deaths. Most patients continued HAART concurrently with the chemotherapy. This study suggests that since the introduction of HAART, HIV-positive individuals with advanced lung cancer may now have a similar outcome as in patients without HIV.

Case series

Burke *et al.* [5] described the diagnosis and prognosis in 4 HIV-seropositive patients who presented with lung cancer (2 squamous cell carcinoma, 1 adenocarcinoma, 1 anaplastic giant cell carcinoma). All were young and were heavy smokers. Although all patients had exposure to HAART, the CD4 counts ranged from 200 to 686 cells/μl, and viral loads ranged from undetectable to 29 000 HIV-1 RNA copies/ml. All patients presented with advanced lung cancer and died within 2 to 9 months of diagnosis. Spano *et al.* [14]

reported on 22 HIV-infected patients with lung cancer; 21 patients were smokers, and the median age at diagnosis was 45 years. Stage III and IV disease was present in 75% of patients. At the time of diagnosis, AIDS had previously developed in 7 patients.

Although most patients with HIV present with advanced lung cancer, aggressive surgical resection for early-stage cancers has been thought to be associated with high postoperative morbidity and mortality, particularly in patients with CD4 counts below 200 cells/mm^3 [15]. Lobectomies with mediastinal lymph node dissections, however, have recently been successfully performed for patients with early-stage disease whose CD4 counts are below 200 cells/mm^3, suggesting that a low CD4 count should not be considered an exclusion criterion for selected patients with surgically resectable disease [16].

One possible reason for the apparently poor outcome in HIV-infected patients with lung cancer may be late diagnosis. Bazot *et al.* [17] reviewed the computed tomographic characteristics of 15 HIV-infected patients with lung cancer. In this series, the main radiographic findings were pulmonary nodules and masses (67% of patients). Four of these patients (2 with low CD4 counts) underwent successful surgical resections of stage I lesions. Of note, percutaneous transthoracic needle biopsy was diagnostic in 7 of the 8 patients who underwent the procedure. Complications included two pneumothoraces (one requiring chest tube placement) and chest wall implantation of cancer in one patient. Given the acceptable pneumothorax rate in comparison with the general population, the authors recommend diagnostic transthoracic needle biopsy for accessible lesions.

Head and neck cancer

Squamous cell carcinoma of the head and neck (SCCHN) represents an anatomically heterogeneous group of neoplasms arising from the mucosal surfaces of the oral cavity, oropharynx, hypopharynx, larynx, sinuses, and other sites within the upper aerodigestive tract. In the United States, approximately 40 000 individuals yearly are diagnosed with this disease, and approximately 10 000 die of the illness [7].

Traditionally the most common cancer in the head and neck region, SCCHN is overshadowed by Kaposi's sarcoma and non-Hodgkin's lymphoma in patients with HIV infection. As is the case with lung carcinoma, however, SCCHN has been seen in excess in HIV-positive populations [3]. The link between HIV and the development of SCCHN is controversial. Possible confounding risk factors among persons with HIV infection, in addition to the traditional risk factors of tobacco and alcohol exposure, include immunosuppression, opportunistic infections, and infection with high-risk human papillomavirus (HPV) subtypes.

Results from case–control studies and case series

Much of our understanding of SCCHN in HIV populations has come from case–control and case series studies. Singh *et al.* [18] published the largest single series of HIV-positive patients with SCCHN. From 1985 to 1994, 24 SCCHN patients with HIV infection were identified from tumor registries of two metropolitan academic tertiary care centers; during the same period, 515 HIV-negative patients with SCCHN presented to the same institutions. There was therefore a 4.5% prevalence of HIV infection among SCCHN patients. Patients with HIV were significantly younger than noninfected patients, but no differences in gender distribution were seen. No significant alteration in the anatomic site distribution of SCCHN primary tumors was noted, with larynx cancer being the most common site, followed by oral cavity and oropharyngeal cancers. Significant exposure to alcohol or tobacco, as defined by the authors, was present in all the HIV-positive patients but was noted in 89% of control individuals. SCCHN tumors in HIV-infected patients were more advanced locally and presented at a higher tumor stage; all cancers in HIV-positive patients were at either stage III or stage IV. Survival was significantly poorer in patients who were HIV positive, even after adjustment for the confounding effects of tumor stage. The relative risk for mortality was 1.5 times that in noninfected patients.

The same group published a small prospective longitudinal study of all patients with SCCHN presenting over a 6-month period [19]. Of the 10 patients with diagnoses of SCCHN, 6 were infected with HIV, and 2 of the patients presented with SCCHN as the initial manifestation of HIV infection. HIV-infected patients were significantly younger than noninfected patients. Although no patient presented with AIDS, nearly all patients with HIV (5 of 6) had an abnormal CD4 count. Treatment-associated complications were common in HIV-infected patients, and the outcome was significantly poorer in HIV-infected patients. In a small series of HIV-positive patients with oral and oropharyngeal cancer (including only 3 patients with SCCHN), Kao *et al.* [20] showed that HIV-positive patients are able to tolerate radiotherapy to these sites. Aside from these two reports with small patient numbers, however, there are no published studies of therapy tolerance and efficacy in HIV-infected patients with SCCHN. Additionally, no information is available on the effect of HAART on patient outcome.

Role of human papillomavirus

Although HPV is known to cause invasive cervical carcinoma (an AIDS-defining cancer), there is increasing molecular and epidemiologic evidence that HPV is associated with a distinct subset of SCCHN tumors, particularly with oral and oropharyngeal cancers. In the published literature, HPV DNA has been identified in 51% of tonsillar (oropharyngeal) carcinomas, most frequently from HPV

type 16 [21•]. Infection of oral exfoliated cells with HPV high-risk types is an independent risk factor for the development of head and neck cancer [22•]. The distinct patterns of genetic alterations observed in HPV-associated SCCHN tumors suggest that HPV 16 infection is an early event in SCCHN development [23•].

The relation between HIV infection and HPV-associated head and neck cancers is complex. Individuals with a history of an HPV-associated anogenital cancer and HIV-infected men are at increased risk for tonsillar carcinoma [24,25]. Kreimer *et al.* [26•] found in a large population of HIV-seropositive and -seronegative adults that the prevalence of oral high-risk HPV infection was greater in HIV-seropositive individuals (13.7% compared with 4.5%, $P < 0.001$). Of note, in multiple logistic regression, the odds of HPV infection increased with herpes simplex virus-2 seropositivity and also with more than one oral sex partner during the previous year. Interestingly, although the use of HAART has resulted in a decreased incidence of oral candidiasis, hairy leukoplakia, and Kaposi's sarcoma, there has been a marked increase in the incidence of oral warts [27]. In contrast to HIV-infected patients with head and neck cancer, it has been suggested that patients with HPV-positive cancers have better survival rates than those with HPV-negative cancers [28•].

Cancer prevention: smoking cessation

The increased risk of aerodigestive cancer in HIV-infected patients has been attributed to smoking, which is more common in patients with HIV infection than in the general population [29,30]. In a prospective study of causes of death among HIV-infected adults in France in the year 2000, 11% of deaths resulted from cancer not related to AIDS or hepatitis (lung cancer was the most frequent cause), and smoking and excessive alcohol consumption were recorded in 72% and 27% of cancer-related deaths, respectively [4••]. Clifford *et al.* [2], in a retrospective analysis of the Swiss HIV Cohort Study, found that although cancers of the lip, mouth, pharynx, and lung were all significantly more common in HIV-positive populations, no cancers from these sites were observed in nonsmokers. Case–control studies for patients with both lung cancers and head and neck cancers have only supported these findings. Given the increased life expectancy of persons with HIV infection, the rates of aerodigestive malignancies are sure to rise. Given the younger age of HIV-infected patients with these malignancies, aggressive smoking cessation efforts are strongly recommended for this high-risk population.

Conclusion

In the era of HAART, although mortality has decreased substantially among HIV-infected people with access to HAART, the incidence of non–AIDS-defining cancers of the aerodigestive tract (lung/head and neck) seems to be increasing. In persons with HIV infection, lung cancer is the most frequently observed and most deadly non–AIDS-defining malignancy. Case–control studies of patients in the pre-HAART era have suggested a younger age of diagnosis and a more aggressive clinical course of both lung cancer and head and neck cancers in patients with HIV infection. Since the introduction of HAART, HIV-positive individuals with advanced lung cancer may now have a similar outcome as in patients without HIV. Whether this is due to improvements in diagnosis and treatment or to a direct effect of HAART (either on immune system reconstitution or in combination with chemotherapy or radiotherapy) on patient outcome is not clear. It is clear, however, that patients with aerodigestive cancers should be treated with disease site and stage-appropriate therapy; there is no evidence to support alternative therapeutic decisions (more aggressive/less aggressive) for these patients on the basis of HIV status alone.

Given that the increased risk of aerodigestive cancer in HIV patients seems to be linked to increased smoking habits, smoking cessation efforts should be targeted to this high-risk population. The role of HPV in the causes of aerodigestive malignancies in persons with HIV/AIDS does not seem to be as tightly linked as it is to its association with cervical carcinogenesis. Nevertheless, the identification of a subset of patients with or at risk for HPV-associated neoplasms may select a population with possible benefit from immune or biologic therapy [31].

Further improvements in the diagnosis and treatment of these patients will likely come from well-designed case–control studies. In the era of active biologic anticancer therapies, the pathobiology of aerodigestive cancers in this patient population is yet unknown and deserves scientific attention. Although clinical trials for HIV-associated lymphoma and Kaposi's sarcoma (AIDS-defining cancers) are increasingly commonplace, there is a need for prospective clinical trials of therapeutic interventions specifically in patients with non–AIDS-defining cancers. With continued improvements in therapies for HIV, the expected increase in incidence and mortality of persons with HIV infection from aerodigestive malignancies will likely become a major public health concern.

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