Lung malignancies in HIV infected patients

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Abstract

Respiratory diseases including malignancies are a significant source of morbidity and mortality among patients infected with HIV. Malignancies such as Kaposi Sarcoma (KS) and Non Hodgkin Lymphoma (NHL) have for long been associated with HIV infection and reduced immunity. In addition to the AIDS-defining malignancies, patients infected with HIV are also at increased risk for developing several non-AIDS-defining malignancies including lung cancer. Electronic literature search for relevant studies was carried out online. Two hundred and seventy five publications were identified by the search. One hundred and thirty two relevant articles were summarized after scrutinizing their abstracts. There is an increased incidence of certain AIDS defining lung malignancies with viral etiologies such as NHL and KS. Likewise other non-AIDS defining malignancies without any clear viral etiology such as lung cancer have demonstrated a rise in prevalence especially in the era of HAART. Immune system dysfunction in HIV infection as well as some peculiar lifestyles has been implicated for this excess risk. HIV patients with pulmonary malignancies generally present late with advanced disease due to delays in making a diagnosis. Diagnosis of lung malignancy in HIV usually involves more extensive diagnostic investigations and invasive procedures. Treatment of lung malignancies in HIV patients is generally similar to the non-HIV patient but with some considerations such as drug-drug interaction, drug toxicity and immune reconstitution inflammatory syndrome. This review will examine the epidemiology, risk factors, diagnosis and clinical management of pulmonary malignancies in patients infected with HIV.

Keywords: Cancer, Acquired immune deficiency syndrome (AIDS), Kaposi Sarcoma (KS), Non Hodgkin Lymphoma (NHL).

INTRODUCTION

Infection with the human immunodeficiency virus (HIV) is associated with an increased risk of developing cancer.¹ Cancers such as Kaposi Sarcoma (KS), Non Hodgkin Lymphoma (NHL) and Invasive Cancer of the Cervix (ICC) have long been recognized to be associated with HIV infection and have been classified as AIDS defining diseases.² In addition to the earlier mentioned AIDS-defining malignancies (ADM), patients infected with HIV are also at increased risk for developing several non-AIDS-defining malignancies (NADM) including lung cancer.³,⁶ With the introduction of highly active antiretroviral therapy (HAART) the survival of people living with HIV infection has continued to improve and HIV infection has transformed into a chronic disease.⁷,¹⁰ Growing numbers of HIV-infected persons are living longer and a changing spectrum of diseases with reduced AIDS-defining conditions but increased non-AIDS disease is being observed.¹¹ Pulmonary diseases remain a significant source of morbidity and mortality even in the era of HAART.¹² These conditions range from infective to non-infective conditions including pulmonary malignancies.¹³ Healthcare workers should be familiar with HIV related pulmonary malignancies, as their incidence is expected to increase further with the rise in the number and survival of HIV patients. The purpose of this article is to review the current data on the epidemiology, pathology and pathogenesis, clinical and radiological presentation as well as the diagnosis and treatment of the important pulmonary malignancies in people with HIV infection.

Methods

The search strategy was conducted using online search engines, without limitation of date, to identify potentially relevant articles. The key words used were;

- “HIV associated lung malignancies” or “HIV related lung malignancies” or “Human immune deficiency virus associated pulmonary malignancies”
“AIDS defining lung malignancies” or “AIDS defining pulmonary malignancies”

“Non-AIDS defining malignancies of the lungs”

“Lung cancer in HIV infection” or “lung cancer” AND “HIV”

Electronic literature search for relevant studies was carried out using Google, Google scholar and PubMed in the following databases; MEDLINE, Popline, global health and web of science as well as organizational websites such as the WHO website. Two hundred and seventy five publications were identified by the search. One hundred and thirty two of such articles were found to be relevant to the topic of review after scrutinizing their abstracts. Full length copies of these articles were obtained and summarized.

**Pathogenesis of HIV associated Oncogenesis**

Cancer originates from genomic alterations that may occur in oncogenes, tumor suppressor genes, and micro-ribonucleic acid (miRNA) genes. These changes are generally of somatic nature; while germ line mutations result in susceptibility to familial cancers for individuals. Oncogenes encode certain proteins that control cell proliferation, apoptosis, or both. Oncogenes are activated by three mechanisms, namely, mutation, gene amplification, and translocation.

Cancers develop in a multistep process involving three main phases: initiation, promotion and progression. Neoplastic initiation is essentially irreversible changes in appropriate target somatic cells. In the simplest terms, initiation involves one or more stable cellular changes arising either spontaneously or induced by exposure to a carcinogen. This is the first step in carcinogenesis where the cellular genome undergoes mutations; creating the potential for neoplastic development. The human DNA sequences that are responsible for transformation are called oncogenes. The transformed cell undergoes continuous division with commitment to the transformed karyotype and, possibly, further mutations may occur, before a malignant lesion is manifested.

The transformed cell can remain harmless, unless it is otherwise stimulated to undergo further proliferation, upsetting the cellular balance. Progression is the process through which successive changes in the neoplasm give rise to increasingly malignant sub-populations. Molecular mechanisms of tumor progression are not fully understood, but further mutations and or chromosomal aberrations may be involved. Repeated exposures to carcinogenic stimuli or selection pressures favouring the autonomous clonal derivatives may accelerate tumor progression. As the transformed cells proliferate, there is a rapid increase in the tumour size. With increasing tumor size, the cells may undergo further mutations, leading to increasing heterogeneity of the cell population.

Studies have shown that every known innate and adaptive immune effector mechanism participates in tumour recognition and control in the interactions between cancer cells and the host immune system. The earliest transformed cells are detected by natural killer (NK) cells through their encounter with specific ligands on the tumour cells. This will leads to the destruction of some of the transformed cells, uptake and the processing of their fragments by macrophages and dendritic cells. These macrophages and dendritic cells are in turn activated to secrete many inflammatory cytokines and present tumour cell-derived molecules to T and B lymphocytes. The activation of T and B lymphocytes leads to the production of additional cytokines that further promote activation of the innate immune system and support the expansion and production of tumour-specific T lymphocytes and antibodies. The full power of the adaptive immune system is thus harnessed and this leads to the elimination of remaining tumour cells and, more importantly, to the generation of the immune system memory to specific tumour components that will serve to prevent tumour recurrence. Effectors of adaptive immunity, such as CD4 helper T lymphocytes, CD8+ cytotoxic T lymphocytes, as well as antibodies, specifically target tumour antigens. Tumour antigens are normal cellular proteins that are abnormally expressed as a result of genetic mutations, quantitative differences in expression, or differences in posttranslational modifications. In tumour types that have a viral origin, such as cervicoviral cancer, caused by the human papillomavirus, or hepatocellular carcinoma caused by the hepatitis B virus, viral proteins can also serve as tumour antigens and targets for antitumour immune response.

The exact role that HIV infection plays in tumorigenesis is not very clear, but HIV is known to cause severe immune deficiency as well as dysregulation of the immune system. This may lead to impaired immune surveillance, increased immune activation and decreased clearance of transformed cells. There is also evidence that HIV directly activates or promotes tumour oncogenes or proto-oncogenes as well as suppresses tumour suppressor genes. HIV has also been found to promote genetic instability and to enhance the susceptibility of epithelial cells to the effects of certain carcinogens. HIV is associated with immune-senescence. This leads to a more rapid immune aging predisposing them to developing cancer.

**AIDS defining lung malignancies**

KS and NHL are AIDS-defining cancers (ADC) and represent the most common malignancies that occur following the development of AIDS. Although the lungs are not typically the primary site of disease, pulmonary involvement for both KS and NHL is relatively common.

**AIDS associated Kaposi Sarcoma (AIDS-KS)**

KS is a multi-centric angio-proliferative tumor of endothelial origin. It is characterized by pathologic and clinical heterogeneity, as well as by the ability to progress or regress based on the host immune status. KS is associated with human herpes virus 8 (HHV8) which is also known as Kaposi sarcoma herpes virus (KSHV). KS was one of the earliest manifestations of the AIDS epidemic. Prior to the HIV epidemic, KS was very infrequent in many parts of the world especially the Western countries with an incidence rate of 0.1 case per one million person-years in Northern Europe and United States of America (USA). Higher rates were observed in Southern European countries such as Spain and Portugal. With the advent of the HIV epidemic, KS incidence quickly increased in Western countries involving mostly young homosexual or bisexual men.

The first case of KS in Africa was reported by Jojot and Laigret in 1922 in present day Cameroun. The authors were impressed that cancers did occur at all among black Africans. In 1962 Oettle estimated the prevalence of KS among cancers to range below 1% in South Africa, Ghana and French West Africa, 2-3% in Nigeria and East Africa having the highest prevalence of 4-10%. With the advent of HIV/AIDS pandemic the reported prevalence of KS has dramatically increased with estimates as high as 50% of all cancers in some reports.

Critical immunosuppression in patients with mucocutaneous KS commonly leads to pulmonary involvement. Thoracic disease is found in about 45% of patients with cutaneous AIDS-related KS, and in about 15% of patients without mucocutaneous involvement. The most common symptoms observed are cough and weight loss which may occur in up to 97% of patients. Progressive dyspnea with fever and chest pain are other symptoms that may be present and hemoptysis may be found in up to 50% of the patients. Physical examination of the thorax is usually normal, but non-specific signs such as crackles, wheezing, and stridor may be present.

The diagnosis of pulmonary involvement in AIDS-KS usually can be made by a combination of clinical, radiographic, and laboratory
findings, along with the results of bronchoscopy and biopsy of lung tissue. Chest radiography may demonstrate reticular opacities and parenchymal nodules with a bronchovascular distribution involving the middle to lower lung zone. This may progress to consolidation, peribronchial cuffing, Kerley B lines, pleural collections, and hilar or mediastinal adenopathies. Rarely the radiograph may be normal.

High resolution computerized tomography (HRCT) scans have more specificity and sensitivity than the chest X-rays. The most frequent CT finding is interstitial thickening, involving the peri-broncho-vascular sheaths, which often begin around the hilum and then progressing to the periphery predominantly involving the middle and lower third of the lungs. There may be associated irregular narrowing of the bronchial lumen due to mucosal lesions. Coalescing of the lesions leads to progressive air-space consolidation. Other HRCT scan findings include interlobular septal thickening, large parenchymal nodules with irregular, poorly defined, and stipulated borders, some of them with a perinodular ground glass halo sign and air bronchograms; fissural nodularity; ground-glass opacities mediastinal adenopathies; and pleural effusions may also be noticed.

Endobronchial AIDS-KS lesions typically consist of single or multiple, red or purple, flat or raised non-stenotic lesions that tend to predominate at segmental junctions in the main bronchi and in the trachea. The bronchoscopic appearance of endobronchial KS is considered to be characteristic enough to allow for a diagnosis to be made.

Treatment of pulmonary AIDS-KS typical involves the use of HAART to improve patient’s immunity. Improved immune response is associated with complete or partial regression of KS lesions, a reduction in the number of patients suffering from KS, improved survival, and enhanced protection of HIV-infected patients against the development of KS. Systemic chemotherapy such as anthracyclines, taxanes, vinca alkaloids, bleomycin, etoposide as single agents, or in combination may be useful for more severe or life threatening diseases. Systemic chemotherapy produces better pulmonary KS specific response but survival is not superior to HAART alone. Newer systemic chemotherapeutic agents such as pegylated liposomal doxorubicin, liposomal doxorubicin, and paclitaxel can be used as single agents and the outcome is similar to combination therapy but with better side effect profile.

Paradoxically, an immune reconstitution inflammatory syndrome (IRIS) may occur in patients with AIDS-KS following improved immunity with HAART initiation. IRIS appears to occur more frequently in patients with AIDS-KS than in patients with other opportunistic conditions and is associated with more severe complications including death, especially in the setting of KS with pulmonary or other visceral involvement.

Non-Hodgkin Lymphoma (NHL)

Severe immunosuppression is the hallmark of HIV/AIDS-associated NHL. AIDS associated NHL most commonly manifests with central nervous system (CNS) involvement in the setting of stage 3 or 4 disease. NHL is an ADC with risk strongly related to the degree of impaired immunity; immunosuppression, often occurring at CD4 cell counts of below 50 cells/ml. Accordingly, AIDS associated NHL has also demonstrated declining rates since the introduction of HAART. Infection with the Epstein-Barr virus (EBV) has been associated with the majority of HIV-associated NHL cases, although the degree of involvement varies in relation to the sub-type of lymphoma. Around 60% of AIDS-related lymphomas are diffuse large-cell lymphomas, typically presenting in the setting of advanced AIDS and at extranodal sites. Burkitt’s or Burkitt’s like lymphoma comprise around 40% of AIDS-related NHL, uniformly express characteristic translocations of the c-myc gene, and may occur at less degree of immunodeficiency than large-cell lymphomas. Primary pulmonary lymphoma (PPL) is an uncommon cause of AIDS-related NHL, and is of the large-cell type with uniform EBV expression. Relative to CNS involvement, pulmonary NHL occurs infrequently in HIV-infected patients. In a review of autopsy records of AIDS patients at two San Francisco hospitals from 1982–1991, 5.8% of NHL patients experienced isolated pulmonary localization without other systemic manifestations, and the lung was the most common organ involved in those with extranodal site of disease in 71% of the cases.

Clinically HIV-infected patients with pulmonary NHL often present with pneumonic or pleural disease; the most common symptoms are constitutional (95%), cough (71%), and difficulty in breathing (63%). A majority of patients have an abnormal physical exam, manifest most commonly by tachypnea (74%). Almost all of the patients will have abnormal chest radiographic findings with lobar consolidation, nodules, reticular infiltrates, and masses in that order of frequency. Thoracic lymphadenopathy may be present, but this is not common. A pleural effusion is seen in a substantial number of the patients. HRCT is more sensitive than chest radiograph and abnormalities that can be detected include; pleural effusion, hilar and mediastinal lymphadenopathy, nodules, lobar consolidation and masses in that order of frequency.

Endobronchial lesions are quite uncommon and as such bronchoscopy and bronchoalveolar lavage (BAL) are not very helpful. Histology specimens are usually obtained by open lung biopsies or percutaneous transthoracic biopsies. Treatment for pulmonary NHL is with chemotherapy using a cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP)-like regimen and in some cases autologous bone marrow transplant. In this era of HAART, the prognosis in AIDS related pulmonary NHL has improved and it approaches that of non-AIDS pulmonary NHL.

Non-AIDS defining malignancies

With the introduction of combination antiretroviral therapy for HIV/AIDS treatment, there has been a significant reduction in the incidence of AIDS-related morbidity and mortality in HIV-positive patients. As a consequence of the restored immune function, the incidence of ADCs has significantly declined, and the prognosis markedly improved. In contrast with the positive impact of HAART on the incidence of AIDS-defining conditions, HIV-positive patients are at increased risk of non-AIDS-related mortality and morbidity. The evidence linking immunosuppression and development of NADCs is not very clear. While some studies showed that a low nadir of CD4 cell count is predictive of an increased risk of developing NADCs, others did not find a correlation between advanced immunosuppression and the risk of developing NADCs.

Primary lung cancer

Lung cancer represents the most frequently occurring NADC in HIV-infected people. Several studies have reported increased rates of lung cancer in HIV-infected patients as compared with uninfected patients. The risk of lung cancer in the setting of HIV infection is elevated for all major lung cancer subtypes. HIV-infected patients are more likely to be current smokers with a baseline history of illicit drug abuse, alcoholism, hepatitis C virus (HCV) infection, and a history of recurrent bacterial pneumonia which are epidemiologic risk factors for lung cancer. Studies have shown that after adjusting for other risk factors such as age, gender, race/ethnicity, baseline COPD, bacterial pneumonia and smoking, HIV infection remains an independent risk factor for lung cancer.

The HIV virus has been postulated to have direct tissue, cellular, or genetic effects that may contribute to the development of cancers, including NADCs. HIV may activate proto-oncogenes, cause alterations in cell cycle regulation, inhibit tumor suppressor genes
such as p53 or cause microsatellite gene instability and genetic alterations leading to tumor initiation. HIV infected tissues may also be more sensitive to the effects of carcinogens from the environment. HIV infection can cause endothelial abnormalities such as pro-angiogenesis signaling, which may enhance the development of tumor growth and distant metastasis.

Immune suppression

Another proposed mechanism for the increased risk of lung cancer in HIV infected population is that the persistent HIV-associated immunosuppression results in impaired immune surveillance and subsequent increased risk for malignancy. The epidemiological data regarding this mechanism is mixed; some studies have shown an association between level of immunity and the incidence of lung cancer. Included in this group is a recent study of a large data base of HIV patients in French hospitals demonstrating a clear dose-response relationship between CD4 count and lung cancer risk, while other studies have not demonstrated any clear association.

HAART

In addition to contributing to prolonged survival and the increased lung cancer risk associated with aging, HAART itself has been suggested to be directly oncogenic and potentially contributing to lung cancer in HIV-infected patients. On the cellular level, nucleoside reverse transcriptase inhibitors (NRTI) such as zidovudine (AZT) and didanosine (ddI) have been shown to elicit mutagenic responses in vitro. Furthermore, AZT and ddI coexpressed potentiated AZT-DNA incorporation and mutagenic responses.AZT when incorporated into host DNA, causes mutations in the hypoxanthine-guanine phosphoribosyl-transferase (HPRT) and thymidine kinase (TK) genes, and induces micronuclei, chromosomal aberrations, sister chromatid exchange, shortened telomeres, and other genotoxic effects in cultured cells. Genomic instability may occur as a consequence of these events.

Monkeys exposed to NRTI in-utero exhibit genotoxic effects which persists after delivery. Transplacental studies in mice have also documented the potential carcinogenic effects of AZT. The offspring of AZT-treated mice presented a significant and dose-dependent increase in the incidence of cancers involving lungs, liver, and reproductive tracts.

Genomic instability which can result from HAART has been hypothesized to increase the risk of lung cancer in HIV infection. Microsatellite alterations a marker of genomic instability, has been detected in significantly higher frequency in HIV infected patients with lung cancer compared with HIV negative patients.

Infection and persistent inflammation

A previous history of pulmonary infections has been associated with increased lung cancer risk in the general population. This is likely related to a chronic inflammatory process. Likewise, pulmonary infections have been theorized to increase the risk for lung cancer among HIV-infected patients. HIV-infected persons are at significantly increased lung cancer risk compared with HIV negative patients.

Cigarette smoking

Tobacco smoking has been shown to be the major etiologic agent in lung cancer. There are well over 5,000 compounds identified in cigarette smoke, including about 73 compounds considered to be carcinogenic to either laboratory animals or humans. Most cigarette smoke carcinogens are substrates for drug metabolizing enzymes. During their metabolism reactive intermediates such as carbocations or epoxides are produced and these electrophilic compounds can react with nucleophilic sites in DNA. This results in the formation of DNA adducts which are critical in the carcinogenic process. If the DNA adducts persist unrepaired, they can cause miscoding during DNA replication and the result is a permanent mutation. If this mutation occurs in a critical region of an oncogene such as KRAS gene or a tumor suppressor gene such as TP53, the result is the loss of normal cellular growth control mechanisms and subsequent development of cancer. Some other tobacco carcinogens directly bind to cellular receptors, some induce chronic inflammation and pneumocyte proliferation.

Considering that smoking is the major etiologic agent of lung cancer, heavier smoking exposure has been considered as the main explanation for higher rates of lung cancer observed in the setting of HIV. Studies have shown that among HIV-infected individuals smoking rates range from 35% to 70%, compared to approximately 20% in the general population in America.

Lung cancer has been reported to occur at a much younger age among HIV patients than in the general lung cancer population with the average age at diagnosis for HIV patients being in the mid-forties compared to above sixty in the general population. Men are significantly overrepresented compared to women, with a male-female sex ratio of about 10:1 this is similar to the general epidemiology of lung cancer. A majority of the patients are symptomatic and diagnosed with advanced disease. The common complaints include cough, shortness of breath, chest pain, fatigue, hemoptysis similar to what is obtained in the general population.

Imaging findings are similar in both HIV-infected and non–HIV-infected patient groups. The majority of these chest radiographs may be reported as either normal or abnormal with nonspecific infiltrates but without an obvious finding to trigger a concern for neoplasm. Among HIV patients with nodular shadows on thoracic CT, only 4% of them were found to have lung cancer. The most common lung cancer findings on thoracic CT is a mass usually T2, the lesions tend to be more peripheral, with most of them in the upper lobes. Extensive pleural involvement without any obvious lung primary may also occur.

Diagnosis of lung cancer is confirmed histologically. Adenocarcinoma appears to be the most common pathologic type of lung cancer among HIV-infected patients, similar to the general population. Survival in lung cancer is generally poor but appropriate therapy may improve patient outcomes. The standard of care for the treatment of early stage non-small cell lung cancer (NSCLC) i.e. cancer stages I – IIIA is surgical resection. For locally advanced lung cancer (some stage IIIA and IIIB), acceptable treatments include chemoradiation and in some instances, surgical resection with chemotherapy and or radiation. Chemotherapy is generally used for metastatic (stage IV) disease. For limited stage small cell lung cancer (SCLC), the standard treatment is chemoradiation with prophylactic cranial irradiation (PCI), whereas for extensive disease, chemotherapy with or without PCI is the treatment of choice.

HIV positive patients with lung cancer are more likely to present with advanced stage disease and less likely to receive treatment. Traditionally lung cancer has a worse prognosis in HIV; a 2-year survival rate of only 10% in patients with HIV, compared with 31% in the general population. Factors that may account for this disparity may include limited access to healthcare, delayed diagnosis and a more aggressive cancer behaviour. On the other hand Rengan et al observed that the overall survival to be similar between HIV positive
patients with lung cancer and HIV negative patients diagnosed between 2000 and 2005. This observation may be due to the positive effect of HAART and a non-detrimental effect of current cancer chemotherapy in the HIV patient with lung cancer. This assumption is corroborated by The Italian Cooperative Group on AIDS and Tumors (GICAT) study to compare lung cancer treatment outcomes in the pre and post-HAART era. The study reported an almost doubling of the median survival of the post-HAART era compared with the pre-HAART era.

Pleural malignancies

Primary effusion lymphoma

Primary effusion lymphoma (PEL) is a rare aggressive lymphoma that is defined as "a large B-cell neoplasm usually presenting as serous effusions without any detectable tumour masses. It is universally associated with KSHV and most times with EBV." PEL occurs mainly, but not exclusively, in HIV-positive patients, who are often middle aged homosexual males. Typically, patients with PEL present with effusions in the pleural, pericardial or abdominal cavities, usually in the absence of an obvious tumour mass, lymphadenopathy or hepatosplenomegaly. Aspiration of the pleural fluid will yield a lymphomatous exudate that is characterized by a very high lactate dehydrogenase (LDH) level. The diagnosis can usually be established by pleural fluid cytology. The neoplastic cells are pleomorphic and show a range of cytomorphological appearances from features of large immunoblastic or plasmablastic cells to those of anaplastic cells. Treatment is similar to NHL but the prognosis is very poor.

CONCLUSION

The increased incidence of certain AIDS defining lung malignancies with viral epidemiologies such as NHL and KS is well documented. Similarly other non-AIDS defining malignancies without a clear viral etiology such as lung cancer have demonstrated a rise in prevalence especially in the era of HAART. Dysfunction of the immune system in HIV infection has been implicated in this as well as some peculiar lifestyles. Patients generally present to the clinician with advanced disease due to late presentation and delays in making a diagnosis. Diagnosis of lung malignancy in HIV usually involves more extensive investigations and invasive procedures. Treatment of lung malignancies in HIV patients is generally similar to the non-HIV patient but some considerations such as drug-drug interaction, drug toxicity and IRIS. Generally treatment outcomes have improved but still poorer than in the general population.

Conflict of interest

The authors declare that they have no conflict of interest.

REFERENCES

34. Restrepo CS, Martinez S, Lemos JA, Carrillo JA, Lemos DF, Ojeda P, Koshly P.


