www.jmscr.igmpublication.org
Impact Factor (SJIF): 6.379
Index Copernicus Value: 71.58
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossrefDOI: https://dx.doi.org/10.18535/jmscr/v6i7.124

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

HIV Infection and Malignancy

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Abstract
HIV-infected individuals have an increased propensity to develop malignancy. The spectrum of neoplasia in these patients is changing, especially in developed portions of the world, where the widespread use of highly active antiretroviral therapy (HAART) has limited the immunosuppression associated with HIV for prolonged periods in most patients. Early in the AIDS epidemic, a dramatic increase in Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and cervical cancer was noted, and these tumors ultimately were classified as AIDS-defining cancers. With the widespread use of potent antiretroviral therapy (ART), there was a dramatic decrease in the incidence of KS and NHL and a significant increase in the incidence of several other malignancies (non-AIDS-defining cancers). An understanding of the epidemiology and risk factors for these malignancies, in association with the prolonged survival of HIV-infected people in the ART era, increases the importance of adherence to cancer screening recommendations and prevention measures. Although the biology of malignancy in HIV infected people is often more aggressive than in those without HIV infection, standard treatment is generally indicated and can be associated with a favorable outcome, depending upon the tumor type, stage, and comorbidity. This paper will review general management considerations for patients with HIV and a malignancy, as well as a discussion of specific malignancies.

Introduction

HIV-infected individuals have an increased propensity to develop malignancy. The occurrence of an extremely high number of cases of Kaposi sarcoma (KS) was noted early in the AIDS epidemic and many of them had an unusually aggressive clinical course. KS was therefore included as an AIDS-defining illness in early case definitions from the Centers for Disease Control and Prevention (CDC). Non-Hodgkin lymphoma (NHL) and invasive cervical carcinoma were subsequently added as AIDS-defining conditions. The spectrum of neoplasia in HIV infected patients has changed in areas where the use of potent antiretroviral therapy (ART) is widespread. The incidence of KS and NHL has decreased markedly, but there has been a relative increase in tumor types that collectively are referred to as non-AIDS-defining cancers (NADCs) compared with the general population. NADCs now are a major factor contributing to mortality in HIV-infected people.

Clinical Implications

Malignancies in patients infected with HIV are often characterized by earlier age at onset, atypical pathology (higher tumor grade), more aggressive clinical behavior, and/or more advanced stage at presentation[1,2]. These features, may have implications for screening and treatment, and may contribute to a poorer outcome, with rapid progression, a high rate of relapse, and a worse response to treatment.

- **Screening and prevention**

The increased incidence of selected cancers in HIV-infected patients, combined with the younger age of onset and the altered biology, raise the question of whether more aggressive screening is indicated[3,4]. Most cancer screening guidelines do not make separate recommendations for individuals infected with HIV, with the exception of the European AIDS Clinical Society[5]. clinicians caring for HIV-infected individuals should make every effort to help patients minimize risk factors for cancer. Potential opportunities include smoking cessation programs, the use of human papillomavirus (HPV) and hepatitis B virus (HBV) vaccines, and the prevention or treatment of HBV or hepatitis C virus (HCV) infections.

- **Principles of treatment**

Treatment of cancer in HIV-infected individuals follows the same general principles as for those not infected with HIV. The diagnosis of cancer should be confirmed pathologically. For patients with early stage disease, initial management is with curative intent, as is the case for non-HIV-infected individuals[2]. Systemic therapy may be required for metastatic disease or as adjuvant therapy. The use of cytotoxic chemotherapy with antiretroviral therapy may result in additive cytotoxicity or other drug-drug interactions and may further enhance immunosuppression. The combination of chemotherapy and ART requires a careful consideration of such potential interactions. Other factors that can complicate the management of malignancy in an HIV-infected individual include the following:

- HIV-infected patients frequently often have significant comorbidities that result in a poor performance status and affect the response to treatment.
- The presence of reactive lymphadenopathy or other imaging abnormalities not related to the malignancy may complicate accurate tumor staging.
- HIV-infected individuals may be poor surgical candidates, because of an increased risk of developing postoperative infections particularly in those with predominantly late stage AIDS. Data from patients with early stage HIV disease found surgical risks were similar to those without HIV infection[6,7].

Aids-Defining Malignancies

There are several malignancies that have been associated with HIV. These include: Kaposi sarcoma (KS), selected types of NHL, and invasive cervical cancer are encompassed in the criteria that define AIDS in people infected with HIV.

- **Kaposi sarcoma**

KS is a low-grade soft tissue sarcoma of vascular origin that is associated with infection with human herpesvirus (HHV)-8 (also known as the KS-associated herpesvirus). Infection with HHV-8 precedes and is predictive of the development of KS. In a study of 800 men, 400 of whom were HIV-positive, the 10-year probability of developing KS was approximately 50 percent in those who were seropositive for both HIV and HHV-8[8]. KS is primarily a disease of men; early in the HIV epidemic, KS was noted in 20 to 30 percent of HIV-infected men who have sex with men. With the widespread use of ART, the incidence decreased dramatically. AIDS-related KS has a variable clinical course, ranging from an asymptomatic incidental finding to explosive growth resulting in significant morbidity and mortality. Skin involvement is characteristic but extracutaneous spread is common, particularly to the oral cavity), lungs and digestive tract. The major goals of treatment for AIDS-related KS are

symptom palliation, prevention of disease progression, and shrinkage of tumor to alleviate edema, organ compromise, and psychological stress. Although there are no randomized trials evaluating the effect of ART, observational studies provide strong evidence that the natural history of KS has changed since its introduction; immune reconstitution due to control of the HIV infection is the most likely explanation for this altered prognosis. ART is recommended for virtually all patients with AIDS-related KS. The need for treatment beyond potent ART and the choice among the various options depend upon the extent of disease, the rapidity of tumor growth, the HIV-1 viral load, the CD4 cell count, and the patient's overall medical condition. Locally directed therapy is often used to palliate symptoms caused by a specific tumor or to treat cosmetic disfigurement. Systemic therapy is used for more extensive disease but injury to an immune system that is already severely compromised should be avoided whenever possible.

- **Non-Hodgkin lymphoma**

NHLs that have been designated as AIDS defining include diffuse large B cell lymphoma, Burkitt's lymphoma, immunoblastic lymphoma, plasmablastic lymphoma, primary effusion lymphoma, and primary lymphoma of the brain. The incidence of NHL in HIV positive patients has fallen markedly since the introduction of ART. NHLs in HIV-infected patients frequently arise in extranodal sites, such as the stomach or esophagus, and may constitute the majority of malignancies seen in those sites.

- **Cervical cancer**

A close association exists between infection with oncogenic strains of HPV and malignancies of the anogenital tract, including the cervix, anus, vulva, penis, and perianal skin. This association has been most thoroughly studied for diseases of the uterine cervix. The vast majority of cervical cancers are thought to be caused by HPV infection. A higher than expected rate of invasive and preinvasive cervical neoplasia has been reported in HIV-infected women[9,10]. Based upon these findings, the CDC in 1993 added moderate and severe cervical dysplasia as an early symptomatic HIV condition (category B) and invasive cervical cancer as an indicator condition in the case definition of AIDS (category C). The incidence of both cervical dysplasia and neoplasia is significantly increased in HIV-infected women, and the prevalence of cervical intraepithelial neoplasia (also called cervical squamous intraepithelial lesions) ranges between 30 and 40 percent[11].

Non-Aids-Defining Malignancies

Many other malignancies have either a significantly increased incidence in HIV-infected individuals compared with the non-HIV-infected population, or have an altered biology with clinically significant implications. These are discussed in this section.

- **Hodgkin lymphoma**

Epidemiology

Hodgkin lymphoma (HL) is among the most common non-AIDS-defining malignancies, with an incidence 15 to 30 fold higher than in the non-HIV-infected population and HL appears to be significantly more common in men who have sex with men compared to those who were intravenous drug users[12]. Features of HL in patients with HIV infection include the following:

- Unfavorable histology is substantially more common in patients with HIV infection. Mixed cellularity HL accounted for approximately 60 percent of cases in two large series [13,14]
- Most patients with HIV-associated HL are EBV positive, with a 75 to 100 percent rate of EBV coinfection. HL tends to develop early in HIV infection.
- The relationship between HL and CD4 cell count is unclear, with some studies indicating that HL is associated with advanced HIV-related immunosuppression[15].
- There is conflicting evidence about the impact of potent ART on the incidence of HL. Some studies suggest that the incidence

has increased in the ART era [16-18], but at least one study did not observe a significant change[12]. The risk of developing HL may be particularly increased in the first months after the initiation of ART[19].

Natural history

Clinically, HL often presents with more aggressive disease in HIV-positive patients than in non-HIV-infected persons. Systemic B symptoms (ie, fever, weight loss, night sweats) are frequent, and widely disseminated extranodal disease may be present in most patients at presentation[20,21]. Up to 40 to 50 percent may have bone marrow involvement at diagnosis. Mediastinal involvement is infrequent in HIV-infected patients. HL of the liver, spleen, and brain have been noted, as well as case reports of HIV-related HL presenting in uncommon gastrointestinal locations such as the anus and stomach [22,23].

Treatment

The optimal treatment for HIV-related HL has not been established in randomized trials. Prior to the introduction of potent ART, treatment of HL was associated with significant toxicity and outcomes were poor[24-25]. Despite the difficulties of intensive treatment in these HIV-infected patients, contemporary regimens have given promising results in several studies [26,27].

Other hematologic malignancies

HIV-infected persons are at increased risk for developing other hematologic malignancies, including plasma cell disorders and leukemia, in addition to HL and non-Hodgkin lymphoma.

- **Plasma cell disorders**

HIV-infected patients can present with a range of plasma cell disorders, including reactive plasmacytosis, paraproteinemia, amyloidosis, light chain deposition disease, plasmacytomas, multiple myeloma, and plasma cell leukemia[28-31]. The incidence of serum protein abnormalities with HIV infection was illustrated by a study of 320 consecutive patients, 16 percent of whom had a detectable abnormality[32].

- **Acute myeloid leukemia**

Case reports suggested that the incidence of acute myeloid leukemia (AML) is increased in HIV-infected persons[33-37]. However, data from the Swiss HIV Cohort study indicate that the overall incidence is similar or only modestly increased [38]. The clinical presentation and biologic features of HIV-related AML are similar to that in HIV-negative persons, although the occurrence of extramedullary leukemic infiltration (myeloid sarcoma) in this setting is not uncommon. In general, HIV-infected patients with AML can achieve complete stable remission with standard therapy. A poor prognosis has been reported, especially with CD4 cell counts <200 cells/mm ^{3}. With increasing use of chemotherapy for both AIDS-defining cancers and non-AIDS defining malignancies, treatment-related leukemiasmay become an increasing issue[39].

- **Hepatocellular carcinoma**

Coinfection with HIV and either the hepatitis B virus (HBV) or the hepatitis C virus (HCV) may be associated with accelerated progression of fibrosis and an increased risk of cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC). In an analysis of over 615,000 individuals infected with HIV, the risk of HCC in individuals who were infected with HIV increased progressively over time, beginning prior to the introduction of ART and continuing up to the present (standardized incidence ratio 3.8 compared with the general population)[40]. An increasing incidence of HCC was seen in the HIV-infected and general population; this was attributed to the incidence and prevalence of HCV and to the longer survival in HIV-infected patients who were treated with ART.

- **Lung cancer**

The incidence of lung cancer is increased approximately two to four-fold for individuals infected with HIV when compared to age- and gender-matched populations[41,42]. This relative increase has remained relatively constant before and after the introduction of ART. There is an increased prevalence of cigarette smoking in the

HIV population[43,44], but the risk of lung cancer remains elevated even after correcting for smoking status[45,46].

The clinical features of lung cancer are illustrated by a retrospective series of 75 HIV-positive patients with lung cancer, who were compared with patients in the Surveillance, Epidemiology and End Results (SEER) database[47]. HIV-infected lung cancer patients were significantly younger (median age 50 versus 68 years). Stage and histologic types were similar to the broader lung cancer population. Aggressive treatment for patients with lung cancer and HIV infection is indicated if the patient's overall medical condition permits. A retrospective analysis compared 322 non-small cell lung cancer (NSCLC) patients with almost 72,000 NSCLC patients without HIV infection[48].

- **Anogenital cancer and premalignant lesions**

Human papilloma virus (HPV) infection has been causally linked with premalignant lesions and invasive cancers involving the anus, vulva, vagina, and penis, as well as the cervix. Malignancies and premalignant lesions in all of these sites are significantly more common in individuals infected with HIV compared with the general population. Management of these lesions follows the same general approach as in non-HIV infected people:

- Anal intraepithelial neoplasia and anal cancer
- Vulvar and vaginal intraepithelial neoplasia
- Carcinoma of the penis

The increased incidence of these lesions may have important implications for screening and the use of HPV vaccine in selected cases. These include:

Head and neck cancer

There is an approximately two- to threefold increase in the incidence of squamous cell carcinoma of the head and neck for individuals infected with HIV, with some variation depending upon the specific site of origin[2,6,41,42]. Other histologic types of cancer may also be increased in the head and neck region, including lymphoepithelial carcinoma of the salivary gland, nasopharyngeal carcinoma, and Merkel cell carcinoma[49]. Common sites of involvement include the oral cavity, tonsillar area, and larynx. The majority of HIV-infected men with squamous cell carcinoma (SCC) of the head and neck are men who have sex with men[50], and the age at presentation appears to be younger than those not infected with HIV[51]. Up to 40 percent of the head and neck cancers in patients infected with HIV are related to human papillomavirus (HPV). Patients with HPV related cancers have a better prognosis than those with tumors that are tobacco-related. Treatment of head and neck cancer follows the same principles as that in non-HIV-infect patients, although complications are more common in HIV-infected patients.

Skin cancers

Basal cell and squamous cell

HIV-infected individuals have a two to three-fold increased risk of nonmelanoma skin cancer (basal cell carcinoma [BCC] and squamous cell carcinoma [SCC])[52]. Factors associated with the development of cutaneous malignancies included increasing age and white ethnicity. BCC is substantially more common than SCC in HIV-infected individuals[53]. This is in contrast to organ transplant recipients, where SCC is more frequent. Unusually aggressive skin carcinomas are a recognized complication of HIV infection [54].

Melanoma

The incidence of melanoma in patients infected with HIV may be moderately increased compared with the general population .Melanomas in HIV-infected patients are often multiple, frequently metastasize, and are associated with a poor prognosis[55]. Hence there is need for a more extensive research for metastatic disease.

Conjunctival cancer

The incidence of conjunctival squamous cell carcinoma (SCC) is significantly elevated in immunosuppressed individuals, including both those with HIV and solid organ transplant recipients[56]. In HIV-infected patients, the spectrum of conjunctival involvement includes intraepithelial dysplasia, carcinoma in situ, and invasive SCC, most commonly originating in the

limbus (transition zone) of the eye. In sub-Saharan Africa, the HIV epidemic has been associated with a dramatic increase in the incidence of conjunctival neoplasia[57,58]. The association of conjunctival SCC with HIV infection in other geographic regions is less well established, although one epidemiologic study has reported an increased incidence in North America as well [59]. Risk factors for SCC of the conjunctiva include age greater than 50 years, high solar ultraviolet radiation exposure, geography (sub-Saharan Africa), and HPV infection[60-62]. Conjunctival SCC in HIV-positive patients occurs much earlier in life than in their HIV-negative counterparts and may be particularly aggressive[63,64]. Presentation ranges from eye irritation or erythema to a plaque or nodular lesion. SCC of the conjunctiva has a high propensity for local invasion into the orbit, and occasionally distant metastases occur. Aggressive histologic variants may be diagnosed, such as spindle cell carcinoma. A biopsy is required to distinguish leukoplakic lesions ranging from pinguecula, to intraepithelial carcinoma (dysplasia, carcinoma in situ), and invasive SCC. Patients with conjunctival cancer will need to be evaluated for eyelid infiltration, intraocular and orbital invasion, as well as metastatic disease. Treatment is mainly surgical[65-67]. Other potential therapies include photodynamic therapy or topical treatment with either mitomycin-C[68,69] or interferon alfa-2b [70,71].

Merkel cell carcinoma and other neuroendocrine tumors

Merkel cell carcinoma is a neuroendocrine carcinoma arising in the skin, which is etiologically linked with infection with the Merkel cell polyoma virus. The incidence of Merkel cell carcinoma is increased more than ten-fold in persons with HIV infection[72-75]. Other extrapulmonary neuroendocrine tumors have also been observed in people with HIV infection. These include cases of carcinoids in both typical locations[76] and unusual sites[77] as well as more highly aggressive neuroendocrine carcinoma[78].

Breast cancer

Infection with HIV has at most a minor effect on the incidence of breast cancer[18,41,42]. However, when breast cancer occurs in HIV-infected women, there appears to be a propensity for bilateral disease, poorly differentiated carcinomas, and early metastasis[79]. The relatively high frequency of these poor prognosis features makes the regular screening of particular importance in HIV-infected women. Despite the tendency to present with more advanced disease, aggressive treatment of early breast cancer can result in a favorable outcome[80].

Gastrointestinal malignancies

- **Colorectal cancer**

Although a 2007 review of the literature composed primarily of patients from the pre-potent ART era did not demonstrate an increase in the incidence of colorectal cancer[42], a more recent study from the United States observed a 2.4 fold increase compared with the non-HIV-infected population for the period 2000 to 2003[41]. An increased incidence of colorectal cancer is also supported by the frequency with which precursor lesions are identified. This was illustrated by a flexible sigmoidoscopy screening study in 2382 patients, including 165 who were HIV positive, in which there was an increased prevalence of adenomas in the HIV population (26 versus 13 percent in HIV negative subjects)[81]. Colorectal cancer may occur at a younger age and be more aggressive in patients infected with HIV [82,83].

- **Stomach and esophageal malignancies**

There is an increased incidence of both stomach and esophageal malignancies among people infected with HIV. In a database analysis of almost 600,000 HIV infected individuals, the incidence of both carcinoma of the stomach and carcinoma of the esophagus was significantly increased compared with the general population (SIRs 1.44 and 1.69, respectively)[84].

Genitourinary malignancies

- **Prostate cancer**

HIV infection does not have a significant effect on the incidence of prostate cancer[85]. Although rare

cases of unusually aggressive HIV-related prostate cancer have been reported[86,87], the HIV status does not appear to influence PSA levels, clinical presentation, tumor grade or stage, or outcome in men with prostate cancer receiving potent ART [88,89]. Furthermore, the use of radiation therapy does not appear to affect the immune system in these patients[90,91].

- **Testicular neoplasms**

There appears to be a modest increase in the incidence of testicular malignancies in men infected with HIV compared to non-HIV-infected men[42]. This increased risk is limited to seminomas and does not appear to affect the incidence of nonseminomatous germ cell tumors [92-94]. Stage at presentation does not appear to be affected by HIV status, and the natural history of testicular neoplasia is similar to that encountered in HIV negative patients. There is no evidence that outcome is worse than in men who have seminoma without HIV infection, and management is the same as in men not infected with HIV [1]. Long-term survival in men appears to depend upon the status of their HIV infection [95-97].

- **Bladder cancer**

There is no evidence to suggest that the incidence of bladder cancer is significantly increased in people infected with HIV[42]. Nevertheless, symptoms of hematuria, dysuria, frequency and/or urgency in an HIV-infected patient warrant complete evaluation, including a work up for bladder cancer.

- **Renal cancer**

In a review of the literature that included seven studies and 444,172 HIV-infected individuals, the relative risk of renal cell carcinoma ranged from 0.8 to 2.0[42]. HIV-infected patients with RCC appear to present at a slightly younger age than those without HIV infection[98]. Those diagnosed with early stage RCC did well after surgical resection, while those who were symptomatic with advanced renal cancer at diagnosis did poorly.

Sarcoma

Sarcomas are uncommon in HIV-infected patients. However, in a review of the literature, there was a disproportionate increase in leiomyosarcoma among those with HIV infection. Leimyosarcoma accounted for 58 percent of all sarcomas other than KS, compared with 17 percent of cases in the SEER database[99]. There may be multiple smooth muscle tumors, often found in uncommon locations such as the CNS, lung, pericardium, pleura, spleen, adrenal gland, lymph node, and orbit[100,101].

Gestational trophoblastic disease

Although HIV is not an apparent risk factor for gestational trophoblastic neoplasia, these patients tend to present with more advanced disease, and may have a significantly worse prognosis than in women without HIV infection[102-103].

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