Infections in Oncology

Infections in HIV-Infected Patients with Malignancy

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Introduction

The 15th year of the human immunodeficiency virus (HIV) epidemic is upon us. During this time, we have seen the onslaught of secondary infections that has made HIV the No. 1 cause of death for persons aged 25 to 44 years in the United States.[1] Within the United States alone, there are approximately 1 million HIV-positive patients, and one quarter of these have the acquired immunodeficiency syndrome (AIDS).[2,3] With the increasing prevalence of HIV infection, better combination treatment regimens, and preventive therapy for opportunistic infections, physicians will be caring for an ever increasing number of survivors with an ever dwindling immune function. The combined risk factors of these diseases present challenges in the evaluation and treatment of infections. The incidence of neoplasia (lymphoma and Kaposi's sarcoma [KS]) increases as the CD4 counts in HIV-infected patients drops -- a phenomenon often concurrent with an increase in opportunistic infections.

Changes in Mortality From HIV Infection and AIDS

We are becoming adept at extending the life of HIV-infected patients, especially those at the end stages of disease. This capability can be attributed to such factors as widespread antiretroviral use and effective prophylaxis against secondary infections. Death rates from HIV disease increase yearly, though an analysis of mortality statistics reveals significant changes in secondary causes of death.[4] Death certificate documentation from 1987 to 1992 indicated a total of 140,461 deaths were related to HIV disease, and the reported annual death rate due to HIV disease doubled (from 10,001 in 1987 to 24,230 in 1992). The leading secondary cause of death was pneumonia from unspecified organisms (17%). Its incidence had not risen; rather, other causes had declined. Specifically, the incidence of Pneumocystis carinii pneumonia (PCP) disease dropped from 32.5% to 13.8%, and slight declines in deaths caused by cryptococcosis and candidiasis were noted. Other causes subsequently increased, including Mycobacterium avium complex (MAC) (12%), cytomegalovirus (CMV) disease (10%), septicemia (11.5%), and non-Hodgkin's lymphoma (NHL) (5.7%). It is likely these changes are due, at least in part, to better prophylaxis, heightened awareness, and improved treatment of specific opportunistic infections (eg, PCP). The proportion of deaths from KS (10.4%) and NHL (5.7%) illustrates the significant fraction of HIV-positive persons who die of cancer.[4]

A study by Katz et al[5] examined the extent of NHL in a cohort of homosexual men from San Francisco. Based on HIV-positive men dying prior to February 1993, they found 12.6% of AIDS patients had a diagnosis of NHL at some point. Although the frequency remains unchanged, the total number of patients involved increases as longevity with this disease increases. This study also reported the significant number of PCP-, MAC-, and CMV-related infections. In this limited population from the San Francisco City Clinic Cohort, the leading initial and lifetime occurrence diagnoses were PCP and KS, both of which are associated with HIV infection and man-to-man sexual contact. PCP and KS affected 66% and 50%, respectively, of the study population. CMV disease and MAC were also significant, comprising 30% and 20%, respectively, of the lifetime diagnoses (Figure). However, the number of deaths of HIV-infected patients due to malignancies other than KS or NHL was not addressed.

In a retrospective review[6] of 565 autopsies comparing two study periods - from 1982 to 1988 and from 1989 to May 1993 - the frequency of PCP was high, but far fewer adult patients with AIDS died with PCP in the 1989-1993 period compared with the 1982-1988 period. The authors determined the frequency of varying diagnoses and the frequency of those resulting in death. Concurring with other studies, this review showed PCP as a decreasing trend but still the most frequent cause of death in both study periods. Fungal infections, including candidiasis and other yeast forms, comprised the next most frequent causes of death in the 1989 to 1993 study period, which is greater than that demonstrated in other reports.[4,5] This discrepancy is explained in part by differences in study methods (specifically, the exclusion of Candida infections[4] or filamentous fungi and non-Candida yeasts[5]). It is also alarming given the improvements in antifungal therapy during this same time period. Analysis of the same data revealed a slightly higher frequency of malignant lymphomas diagnosed between the study periods - from 12.9% in 1982-1988...
We are better able to extend the survival of patients with AIDS, despite their profound immunosuppression. Median survival increased from 12 months to 20 months during the first decade of this syndrome,[5] and living with AIDS has been positively associated with retroviral therapy since 1988.[6] Our improved ability to care for and extend the lives of patients with HIV infection, however, also increases the complexity of care associated with these patients. This supports previous reports that anticipated an increase in lymphoma incidence as therapy for HIV disease improves.[7] Although patients with both HIV disease and cancer represent a small percentage overall, they will present an increasingly common challenge for physicians.

Tumors and HIV Infection

AIDS-Defining Tumors

Since 1991, over 2,500 entries focusing on HIV infection and neoplasms have been added to the MEDLINE database. Currently, only three types of malignancy in the setting of HIV disease denote a diagnosis of AIDS regardless of CD4 counts: KS, high-grade B-cell and primary central nervous system NHLs, and invasive cervical carcinoma. All are associated with progression of immunosuppression from HIV disease, have a significant clinical impact on patients, and are treatable with current methods. The most prevalent tumors are KS and NHL.

Kaposi's Sarcoma

The association of KS and homosexual acquisition of HIV infection has been recognized since the early years of the epidemic.[8] KS remains the most prevalent of all HIV-associated malignancies. Skin is the most common of a variety of body sites that can be involved (Table 1). Geographic distributions, possibly influenced by cultural sexual practices, also have been documented. KS occurs primarily in men practicing receptive anal intercourse. A plausible explanation for this epidemiologic finding has been recently reported in the discovery of a KS-associated herpes virus.[9]

Several attempts have been made to stage KS in patients with AIDS.[10,11] Patients are assessed on functional status, the extent of tumor involvement, and the degree of immune suppression. Poor prognostic factors include visceral organ involvement, a CD4 count of less than 200 cells/µL, and evidence of other systemic illness.

AIDS-Defining Lymphomas

Autopsy studies have shown the most common sites for all types of lymphoma (besides lymph nodes themselves) are the lung, biliary tree, central nervous system, spleen, kidney, and small and large bowel (Table 2).[6] Since 1985, the Centers for Disease Control and Prevention has included high-grade B-cell and central nervous system lymphomas as AIDS-defining illnesses. Epidemiologic studies show an increased risk of NHL (198-fold) in HIV-infected patients who have a previous diagnosis of KS.[12] A small subset of HIV-associated lymphomas, the so-called body-cavity-based lymphomas, have been identified with KS-associated herpes virus.[13] Several reports document the association between HIV infection and lymphoma, its occurrence with later stages of HIV disease, and the generally poor outcome.[7,14,15] These patients typically present with accentuated clinical findings compared with their uninfected counterparts. The specific symptoms are related to the organs involved, with a majority of patients having extensive involvement at presentation. "B" symptoms are common, with fever predominating. Sources of fever can be difficult to discern due to the broad spectrum of both common and opportunistic infections occurring in patients with advanced HIV disease.

Other Malignancies

In addition to the previously named AIDS-defining tumors, a variety of lymphoproliferative malignancies, squamous cell carcinomas, germ-cell tumors, and malignancies of the alimentary tract have been reported in HIV-infected patients.[16-18] As control of HIV infection improves and as patients age, malignancies common in the uninfected population will be encountered.

Hodgkin's Disease

The increased incidence of Hodgkin's disease with HIV infection has received special interest,[19-21] although the risk is negligible in comparison to KS and lymphoma. Patients typically present with advanced disease, have aggressive histologic subtypes, and respond poorly to therapy.[22] In two studies,[19,21] totalling 64 patients with Hodgkin's disease, 42 developed an opportunistic infection. PCP predominated, occurring in 16 patients. Other entities included pulmonary Mycobacterium tuberculosis (12), esophageal candidiasis (9), MAC (7), and CMV disease (3). Syphilis was recorded in two patients and should be considered in all patients infected with HIV. Syphilis is easily overlooked in hospitalized cancer patients.

HIV infection resulting from intravenous drug use has been associated with the development of Hodgkin's disease.[21,23] In a comparison of HIV-infected and -uninfected patients with Hodgkin's disease, age appeared to be a differentiating factor, with HIV patients presenting in the third and fourth decade of life (median age = 33 years).[19] Patients with Hodgkin's disease usually present with a bimodal age distribution (less than 35 or more than 50 years of age). In the future, this lymphoma subtype may be recognized as an AIDS-defining illness.

Lung Carcinoma

Carcinoma of the lung is an unusual occurrence in patients with HIV infection. In a review by Flores et al.[24] adenocarcinoma was identified as the predominant histologic type of primary lung malignancy in HIV-infected patients. HIV-positive patients with lung carcinoma had an earlier age of onset (mean age = 48 years), more advanced disease at presentation, poorer response to treatment, and shorter survival (median = three months) than their uninfected counterparts. Most of the 19
patients were smokers and had AIDS with a median CD4 count of 121 cells/µL at diagnosis. Mucocutaneous candidiasis (eight patients), PCP (five), and M. tuberculosis (six) were the most commonly reported infections. Syphilis was found in seven patients, which emphasizes the importance of screening for other sexually transmitted diseases, including hepatitis B and C. Surprisingly, 13 patients were diagnosed with lung cancer either before (two patients) or within one month (11 patients) of the diagnosis of HIV infection. Several issues (eg, economic status, access to health care) may have influenced the finding of advanced stages of disease at diagnosis of lung cancer, but advanced disease stages with aggressive tumor subtypes are more common in younger age groups. The association of PCP and pulmonary M. tuberculosis was reinforced in an expanded study [17] in which patients typically presented with a peripheral nodule in the upper lobes and a history of PCP or pulmonary M. tuberculosis. The issue of optimal therapy, particularly surgical resection, has yet to be addressed in this population of patients. Although they comprise a small subset of HIV-infected patients with cancer, patients with lung carcinoma present unique challenges in selecting modalities of therapy and in treating concurrent pulmonary infections.

Germ-Cell Tumors

An uncommon but highly treatable disease in HIV-infected men is cancer of germ-cell origin.[18,25] The peak incidence of both HIV disease and testicular cancer overlaps (20 to 35 years of age). At present, no evidence is available to confirm an increased incidence of germ-cell tumors in patients with HIV infection. These tumors remain an important entity, however, due to their epidemiology, their positive response to combined modality therapy, and the apparent lack of HIV progression during or immediately following treatment.[18]

Risk Factors for Infection

The onset of infection represents an imbalance of host immunity and the combination of pathogen virulence and quantity. Risks associated with the unique population of HIV-positive patients with cancer are outlined.

Neutropenia

Defective cellular immunity is the most significant risk factor for infection in patients with HIV disease and cancer. Reduction in the circulating absolute granulocyte count (AGC <500 cells/µL) in both populations is common during the later stages of disease or while undergoing cytotoxic therapies. Risk of infection from both opportunists and endogenous microorganisms is exaggerated during this period, especially when profound neutropenia occurs (AGC <100 cells/µL). Causes of neutropenia include decreased production of white cells from marrow suppression, impaired granulocyte function, or increased destruction and sequestration (Table 3). Neutropenia is a major toxicity that limits chemotherapy dosage. HIV-infected patients are not spared this complication, and recent trials have shown neutropenia to be a dose-limiting side effect.[26] The risk of infection in neutrophilic patients due to HIV disease has been questioned by Farber et al.[27] These investigators found no significant difference in frequency of infections during neutropenia and nonneutropenic periods in the same patients. Limitations of this study are the higher than usual level of AGC (1000 cells/µL) used to define neutropenia, the clinical association of fever, and its anecdotally defined neutrophil counts for support. However, a higher incidence of bacterial infections was noted in patients with neutropenia attributed to hematologic malignancies when compared with HIV-infected neutropenic patients.

The more complex issue of neutropenia associated with antineoplastic chemotherapy also has been addressed.[28] Hambleton et al.[28] found no additional risk of bacteremia or death associated with chemotherapy vs other causes of neutropenia in HIV-positive patients. Poor outcomes were associated with sepsis, pneumonia, and bacteremia; their most common blood isolates were Escherichia coli, viridans streptococci, and Staphylococcus aureus. In the neutropenic patients not receiving chemotherapy, all had CD4 counts of less than 200 cells/µL. In a more recent study[29] of HIV-infected patients with varying degrees of neutropenia (AGC <1000, <750, and <500 cells/µL), patients were matched for HIV staging based on CD4 counts. Individual bacterial infections were similar in the two studies; however, bacterial infections were more common in neutropenic patients, especially when the AGC was <500 cells/µL (relative risk = 7.92).[29]

Disruption of Mechanical Barriers

Defects in the natural immune barriers of skin and mucous membranes are important contributors to infection in patients with HIV disease and cancer. The more familiar scenarios are mucositis from cytotoxic agents or iatrogenic penetration of the skin for vascular catheterization.[30] Mucositis and stomatitis in HIV-infected patients may have several causes. Mucosal damage may be caused by cytotoxic agents or antiretroviral drugs, or it may be induced by agents used for prophylaxis (eg, trimethoprim-sulfamethoxazole and dapsone). Infectious mucositis from Candida sp, herpes simplex virus (HSV), and CMV disease occurs in late-stage AIDS.

A unique concern in HIV-infected patients with cancer is mucosal damage from tumor involvement of the alimentary or respiratory systems, as well as the high microbial nucliec contained within. KS occurs frequently in these organs.[6] Campylobacter bacteremia has been associated with gastrointestinal KS.[31,32] External-beam radiation therapy can produce mucosal erosions, and increased radiation sensitivity of mucous membranes in HIV-positive patients has been anecdotally reported.[33,34]

Nutrition

The importance of nutrition in maintaining immune function is often underemphasized in the management of severely compromised patients. For patients with HIV infection, this problem is often compounded by “wasting disease” in the later stages of AIDS. Mortality is closely allied with loss of lean body mass.[5] Supplementation of calorie nutrition is recommended. Either intravenously or via enteral feeding tubes, although use of these methods contributes to the risk of infection. The complex issues involved in ensuring adequate nutrition for HIV-infected patients with cancer require a multidisciplinary management approach. Early recruitment of dietitians to assess progress in protein-calorie nutrition is recommended.

Because of its ready availability for abuse and the ability to replace calories without protein and other nutrients, the recreational drug ethanol is unique compared with other habitual substances[35] and must be considered in initial nutritional evaluations.
Specific Pathogens

Opportunistic infections and their relationship to progressive immune dysfunction in AIDS are well documented.[36] Table 4 outlines the more common opportunistic infections and the CD4 counts at which they tend to occur. A difficult issue in the clinical evaluation of HIV-infected cancer patients is establishing if a problem is related to the HIV infection, to the underlying malignancy, or to both. Kuruvilla et al.[37] describe an AIDS patient with coexistent oral cryptococcus and KS, despite systemic therapy with amphotericin B. In another case, histoplasmosis has been demonstrated in KS lesions.[38] These two cases illustrate the possibility of tumor (KS in this case) rendering antimicrobial therapy ineffective. Bacillary epithelioid angiomatosis (BA) can be confused with KS. In a report by Steeper et al.[39] new lesions involving the viscera were initially attributed to KS. Subsequent special staining techniques proved BA involvement, which responded to antimicrobial therapy. Although KS was a background diagnosis, the importance of monitoring for other HIV-associated pathogens must be emphasized. Commonly associated with cutaneous lesions, both KS and BA can be found in bony structures, with BA predominating. Isenberg and Aronson[40] recently compared the osseous involvement of KS and BA and found that fever and bone pain were more common in BA. CMV disease can even masquerade as pulmonary nodules in an AIDS patient with NHL and KS,[41] thereby adding to the already extensive list of infections and neoplasms associated with pulmonary infiltrates in AIDS. Even common opportunistic infections in HIV can have unusual presentations when combined with malignancy. Histopathologic and microbiologic evaluations are necessary for reliable diagnosis.

Therapy Strategies

Prophylaxis

General recommendations for the prevention of opportunistic infections in HIV have been established by a joint consensus from the United States Public Health Service and the Infectious Disease Society of America.[42] The strongest evidence supports systemic therapy with oral trimethoprim-sulfamethoxazole for both primary PCP and toxoplasmosis reactivation. Due to the close association between pulmonary M. tuberculosis and AIDS, routine screening with purified protein derivative is recommended, especially for HIV-infected cancer patients who typically have advanced disease. Anergic patients with risk factors for tuberculosis exposure should consider taking isoniazid therapy for 12 months. Other regimens are tailored to the tolerance of the antimicrobial agents and the local prevalence of a specific opportunistic pathogen. Beyond antimicrobial therapy aimed at specific pathogens, this report promotes strategies to avoid exposure to likely pathogens.

Vaccination against pneumococcus and hepatitis B for high-risk, susceptible patients is recommended. Annual influenza vaccinations are recommended to reduce the predisposition to secondary bacterial pneumonia and sinusitis. Vaccination against Haemophilus influenzae also can be considered.

Antiretroviral Therapy

Recent elucidation of the rapid kinetics of HIV infection offers a compelling argument for continuing antiretroviral therapy during hospitalization for acute illness or administration of cytotoxic chemotherapy or radiation therapy.[43,44] Previously, antiretroviral therapy was commonly suspended during such periods. The myelotoxic effects of zidovudine, the most widely used antiretroviral agent, have been a concern, especially in cancer patients undergoing cytotoxic therapy. Newer antiretroviral agents are generally not myelotoxic and can safely be used during cancer chemotherapy. Cytokines, such as recombinant erythropoietin and granulocyte colony-stimulating factor, also reduce myelotoxic effects in HIV-positive patients.[45,46]

References
