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HIV Infection, Immunity, and Cancer

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I. INTRODUCTION

One of the earliest manifestations of the AIDS epidemic was the abrupt increase in the incidence of Kaposi's sarcoma (KS; 1). Later review of cancer statistics showed KS diagnoses in young, single men to be a sensitive indicator of when the HIV epidemic first entered homosexual communities. In New York City the incidence of KS started to increase in 1977, at least 3 years before acquired immunodeficiency syndrome (AIDS) was formally recognized (2). The significance of these few cases was missed at the time because they were seen by different caregivers and because cancer registry data takes several years to be compiled and analyzed.

The appearance of KS provided an important clue to the pathogenesis of AIDS. Studies done long before the AIDS epidemic had documented that the incidence of KS was high in immunosuppressed persons (3). Almost from the onset of the AIDS epidemic, studies of phenotypic and functional immunity in persons with AIDS documented profound deficits of cellular immunity. Furthermore, prospective studies of persons at risk of AIDS, usually homosexual men, noted that HIV-infected subjects had, over time, progressively impaired cellular immunity that led to fatal opportunistic infections and cancers (4). Even before the human immunodeficiency virus (HIV) was discovered, these data were able to establish that the cause was likely to be infectious, and that the probable routes of transmission were sexual and bloodborne. These hypotheses were confirmed after the causal agent, HIV-1, was finally determined in 1983–1984.

II. HIV-1

The virus HIV-1 is a member of the lentivirus family of retroviruses. Other members that infect humans include HIV-2 and the human T-lymphotropic virus (HTLV) types I and II. As a group, these viruses are characterized by being RNA viruses that carry the enzyme reverse transcriptase within the viral particle. This enzyme translates the RNA virus genome into a DNA form that is transported into the nucleus and randomly inserted into the host DNA. Once there, the DNA instructs the replication of viral components, which are assembled in the cytoplasm and emerge from the cell membrane as new virus particles.

Although the HIV and HTLV groups of viruses are quite distant from each other (less than 5% homology), they share structural similarity in the placement of gene sequences as well as operational similarity. The major antigens recognized by antibodies are the Gag (involved in binding the RNA core), the Env proteins (involved in the envelope surrounding the intact virus), the enzyme reverse transcriptase, and various regulatory proteins that control the production and assembly of the virus. Although beyond the scope of this book to discuss these in detail, they may appear in the context of reports of antibody results and are potential targets for virus-specific therapies.

A. Viral Entry and Tropism

The virus was initially thought to attach to CD4 receptors on the cell surface (5). However, recent investigators have shown that viral binding involves at least two chemokine receptor sites, CCR5 and CXCR4 (6–8) in addition to CD4. These coreceptor sites are essential for infection, as indicated by the fact that persons who have genetically determined losses of these receptors are rarely infected (9), although there are exceptions (10). Surface receptors may help determine the tropism of the virus to certain cells. Macrophages (11) and glial cells (12,13) have both CD4 and coreceptors, rendering them susceptible to infection. Although unproved, strain variation in the ability of the virus to enter cells of specific types could influence clinical manifestations.

B. Reverse Transcriptase and Error Production

A major growth characteristic of HIV-1 is the high rate of replication and mutation, with over a billion new virions produced each day. It has been estimated that only a small fraction of the viral particles produced are complete and capable of infecting another cell (14,15). With large numbers of viral particles coming from each cell before its death, this replication rate is sufficient to create a constant proliferation over the entire time course of infection (16,17). Soon after initial infection there is an initial high level outburst of viremia, but by 1 year

after infection, viral levels become established at a somewhat lower level. These levels increase slowly over time, rising particularly at the end stages of AIDS illness (18,19). High viral load levels are established in the initial years after infection and are associated with a more rapid onset of immunosuppression and subsequent AIDS-defining illnesses, probably including cancers (20,21). Fortunately, chemotherapy given to HIV-infected patients with cancer does not affect viral levels (22).

This high rate of replication has several implications. Reverse transcriptase, the enzyme used to convert viral RNA to the DNA form, is error-prone in its copy fidelity (23), which no doubt contributes to the relative low number of complete, infectious viral copies. However, the error-prone nature of the enzyme also introduces variations in the virus, such that within the same host, many new variants emerge from the initially infecting strain over time. Whether a particular variant becomes the dominant strain is a consequence of enhanced replication by the more efficient subtypes and of immunological pressure, since the residual immune system recognizes and responds to the presence of the emerging variant. Furthermore, there is controversial evidence that the HLA type of the host could influence the immunological control of the virus (24,25).

Within individuals and transmission-linked groups, the variants ("quasi-species") are closely related genotypes (26). However, in distant populations, new subtypes emerge. By definition, subtypes, also called clades, are more than 10% different from other viral types. In North America and Europe, the B subtype is the dominant clade (27), but in other geographic areas, different clades predominate (28). In some areas, two or more subtypes are circulating in the same population (e.g., A and D in East Africa and B and E in Thailand), which implies at least two sources of the infection for these populations. At least one subtype, found in central Africa, termed type O, is sufficiently divergent that infected persons may escape detection by standard antibody tests (29). The clinical significance of these subtypes is unknown.

C. Antiretroviral Therapies

The variations of the viral quasispecies within an infected person can lead to the emergence of strains resistant to antiretroviral therapies. Zidovudine (AZT), the first drug shown to have a significant antiretroviral effect, is a thymidine analogue that competes for reverse transcriptase. Patients treated with AZT typically have an initial measurable decline of viral load by 1/2 to 1 log. Surprisingly, this minimal effect is associated with clinical improvement. However, because of emerging resistant subtypes, the clinical benefits wane within a few months, and viral load returns to the previous levels (30–32).

Because of this rapid emergence of resistance, the current clinical approach to therapy advocates the simultaneous use of multiple agents, each acting against

a different viral target, such as reverse transcriptase and the viral proteases, with the objective of stopping all viral replication so that resistance cannot emerge. Since 1995, several new drugs have become available for clinical use (33–35). These fall into two groups, the nucleoside analogues and the protease inhibitors. Although each alone may be only marginally, if at all, better than AZT, their benefit lies in the combination usage. As they have different toxicities, they can safely be given together at tolerable doses, while at the same time effectively reducing viral replication to the point that HIV cannot be detected in peripheral blood samples. In such patients, CD4+ lymphocyte levels typically improve (37). Even though functional immunity is not fully restored, the patients usually show clinical benefit relative to opportunistic infections (38), leading to longer survival (39) and a decline in deaths caused by AIDS (40).

Despite their potential efficacy, wide-scale application of these new combination therapies will be difficult. Persons with limited mental or physical abilities, including those with advanced HIV-related conditions, have difficulty complying with the complex regimens, which require the use of several drugs, each given on different schedules. Furthermore, the subjects must be monitored for potential side effects of these therapies. Finally, the expense of such therapy, which currently can cost up to \$30,000/year per patient, may be prohibitive. Certainly, such therapies will not be applicable to many developing countries where millions of people are HIV-infected but health care is limited by financial constraints.

For such countries, prevention strategies, including vaccines, will be the only practical approach. Prevention efforts have shown some success in many parts of the developed and developing world, but so far, vaccine progress has been disappointing. Many factors contribute. There is almost no evidence to demonstrate that infected persons might rid themselves of established infections through their own immunological response. "Therapeutic vaccines," which are given in the hope of slowing progression in persons already infected, are under evaluation but have not yet been shown to be effective. However, preventive vaccines, which are aimed at preventing primary infection, present a difficult immunological problem and safety concerns that will require separate approaches to design and testing.

III. IMMUNITY

Following initial infection, there is a period when the virus is below the threshold of detection. Thereafter, a burst of viremia emerges, sometimes associated with acute but nonspecific symptoms, called the acute retrovirus syndrome or HIV seroconversion syndrome (Fig. 1) (41,42). Over several weeks to months, viral loads usually decline, presumably because of host immunity. This early infection is reflected in changes in the immune system, with the loss of about a quarter to

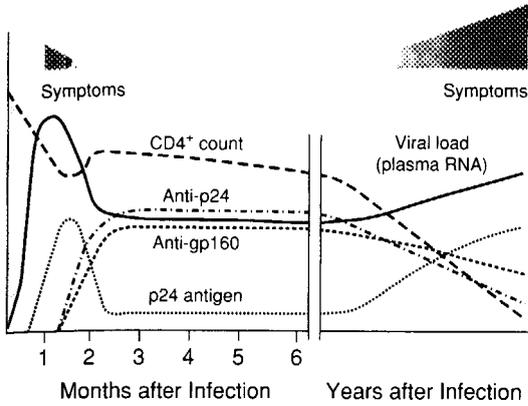


Figure 1 Schematic presentation of changes in virological and immunological parameters in relation to HIV infection and symptoms related to infection. The early symptoms are related to the initial viremia and described as “flu-like,” often with a lingering lymphadenopathy. As immunity deteriorates in the years following infection, symptoms are related to opportunistic infections and malignancies. (From Ref. 68.)

a third of the CD4 cells in the peripheral circulation (43). Thus, the typical levels of CD4 cells are about $900/\mu\text{L}$ before infection, but within a year, cell levels are close to $600/\mu\text{L}$, with persons who have a more dramatic decline having a faster course of subsequent immunosuppression. Thereafter, in the absence of antiretroviral therapies, the CD4 cell count will fall by $40\text{--}50/\mu\text{L}$ per year on average. After a median time of 8–9 years after infection, infected persons have about 100–200 cells per microliter, a level at which immunodeficiency-related illnesses start to occur (44,45).

The rate at which CD4 cell counts decline varies considerably among individuals. In addition, there is variation in the CD4 count at which immunodeficiency-related illnesses may occur. Having a high viral load 1–3 years after infection is a harbinger of faster CD4 cell count decline, but younger-aged persons develop AIDS at slower rate, even after adjusting for viral load (which does not appear to be age-related; 22). This may occur because CD4 stem cell replication capability is greater in the young, resulting in a slower rate of CD4 decline. Furthermore, young persons have fewer AIDS illnesses, even at the same level of immunodeficiency, probably because the young have had fewer exposures to environmental pathogens that might be reactivated with immunodeficiency. Interestingly, after adjusting for the CD4 cell count, increasing age was associated with an increased risk of AIDS-associated cancer, but not opportunistic infections in one study (46).

A. Implications for Cancer Epidemiology

The application of these observations to cancer epidemiology will be discussed in Chapter 3. Both KS and non-Hodgkin's lymphoma (NHL) require a setting of immunodeficiency to become manifest in HIV-infected patients. Thus, the HIV epidemic necessarily precedes the epidemics of associated cancers by several years. Because the number of persons with HIV-related immunodeficiency can be only estimated, the relative risks of these cancers have been compared with the expected rates in the general population. Therefore, relative-risk estimates become higher as the HIV epidemic matures and a higher proportion of HIV-infected persons are severely immunosuppressed. Among untreated persons, this trend will continue until the numbers of persons with HIV-related immunodeficiency reaches a steady state.

The advent of highly active antiretroviral therapies (HAART) will impinge on cancer risk both directly and indirectly. Two reports describe regression of already established KS in patients who responded well to antiretroviral therapy (47,48), presumably because of the improvements in immunity. Such remissions have previously been well documented in patients iatrogenically immunosuppressed, among whom reduction or cessation of immunosuppressive therapies have cured or caused regression in an established malignancy. The new therapies are also likely to reduce the incidence of cancer in HIV-infected persons. There is preliminary evidence that the incidence of KS in treated persons is already declining below that expected (38). In unpublished work described during a round table discussion at the second National AIDS Malignancy Conference, Washington, D.C., April 6–8, 1998, investigators suggested that the incidence of primary brain lymphoma has declined as well.

Presumably, if immunity were completely restored, the excess risk of cancer would entirely disappear. However, the cancer–incidence response pattern could be complex. If the deterioration in immunity is held at a level of only partial improvement, it is possible that, even though opportunistic infections are controlled and KS incidence is reduced, lymphomas might continue to be generated as the lymphoid system compensates for an ongoing, but smoldering, destructive process. The full effect of these therapies on cancer risk will require more follow-up time.

B. Cancer in Non-HIV-Related Immunodeficiency

When the AIDS epidemic first appeared in the United States, KS was a prominent manifestation in many of the earliest cases. This cancer, otherwise rare in the United States (49), had already been noted to occur in excess in organ transplant recipients who had been iatrogenically immunosuppressed to prevent rejection of transplanted tissue (50,51). Thus, its epidemic appearance in previously

healthy young men was immediately recognized as a manifestation of an underlying epidemic of an acquired immunosuppression. However, KS was not the most common tumor associated with transplant-related immunosuppression, leading to concerns that other cancers would soon appear in AIDS patients.

Lymphomas were the most frequent tumor in the setting of iatrogenic immunosuppression (52–54), and they are also known to occur in rare genetic immunodeficiency syndromes (55). Lower, but still important, excess risks of many other tumor types (summarized in Ref. 56) have also been reported. Other frequently mentioned cancers in transplant recipients include lip and other skin (including squamous and basal cell carcinomas and melanoma) and renal and bladder cancers, but there are a variety of other cancer excesses reported. Overall, the 10-year risk of cancer in organ transplants is about 15–20%, providing a relative risk of about four to five fold compared with a general population of the same age (54,57).

Among patients in the United States, the median time to cancer onset after the onset of immunosuppressive therapy is about 22 months for KS, 32 months for NHL, and 67 months for other tumors (58). However, some cancers, especially KS, can appear within a few months of the onset of immunosuppression. As immunosuppressive regimens have become more powerful, the incidence of lymphomas in treated patients has risen, and the time to onset is generally more rapid (57,59–61).

Although the absolute risks of KS in transplant patients are much lower than for NHL, the relative risks are higher because KS is much rarer than NHL in the young persons typically undergoing transplantation. Unlike NHL risk, the KS risk varies geographically. Specifically, in a Scandinavian study, only 2 cases of KS were seen in 5692 renal transplant recipients (54), whereas in the United States, 307 of 7192 organ transplant patients developed KS (58). This variation indicated the existence of regionally distributed cofactors. The newly described human herpesvirus-8 may account for much of this variation (Chapter 3). Marrow transplant recipients are also at excess risk of malignancies, about half of which are NHLs, which tend to occur within the first few years (62). The relative risk of KS is increased, but the absolute risk is low; only 1 of nearly 20,000 marrow transplant recipients developed KS (63).

Even though transplantation-related cancers clearly occur in the setting of immunodeficiency, it is unclear if the malignancy can be attributed to immunosuppression alone. Many other factors may contribute, such as events causing the underlying condition necessitating the transplant, treatment with potent carcinogenic drugs and radiation that are used therapeutically, chronic antigenic stimulation provoked by the presence of the foreign transplanted organs, and for marrow transplants, the occurrence of graft-versus-host disease (GVHD) from imperfect matches. Bone marrow transplant recipients offer a good example. These patients may receive transplants following marrow ablation of the underlying

ing leukemia and, therefore, have exposure to multiple potentially carcinogenic agents, including chemotherapies and radiation, in addition to immunosuppressive regimens to prevent rejection of the transplanted marrow. In this setting, excess risks of thyroid and brain tumors appear to be related to radiation, whereas graft-versus-host reactions were associated with squamous cell tumors of the buccal cavity and skin (63). Melanoma risk is also excessive, but it is not specifically associated with any known factor (63) and may also occur in excess in organ transplant recipients (64). These forms of cancer do not appear to be excessive in AIDS patients. Of interest, NHL risk in patients with renal transplants is associated with cadaveric (rather than sibling) kidneys, and with having multiple transplants, raising the possibility that antigenic stimulation could be related to the etiology (65).

Possibly, immunosuppression adds an additional factor that increases tumor expression in these settings. Regression or even remission of both KS and NHL has been reported after discontinuing immunosuppressive therapy (66,67). These observations strongly suggest that immune function may affect tumor expression, even after the emergence of the tumor.

IV. SUMMARY

Although some of these findings have become evident only in recent years, the occurrence of NHL and KS in immunosuppressed persons was well established before the AIDS epidemic. Finding excesses of KS and NHL, therefore was, consistent with the other laboratory and clinical evidence of immunodeficiency in AIDS. However, NHL and KS are not the only tumors to occur in other settings of immunodeficiency. The possibility that these other tumors might also appear among AIDS patients raised the specter of a broad-based epidemic of multiple cancers of many different types in conjunction with the emerging AIDS epidemic.

Fortunately, only a limited number of cancers have so far been associated with HIV-AIDS (68,69). Although it is still possible that new cancer associations will be discovered as larger numbers of people survive long-term with HIV-related immunodeficiencies, it is unlikely these cancers will occur in large numbers. Nevertheless, any relations found may lead to important new understandings of the pathogenesis of these malignancies.

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