Immunopathogenesis of Human Immunodeficiency Virus Infection

Harry L. Ioachim

Departments of Pathology, Lenox Hill Hospital, Cornell University Medical College, and College of Physicians and Surgeons, Columbia University, New York, NY 10021

Abstract

The acquired immunodeficiency syndrome (AIDS) is associated with a broad spectrum of opportunistic infections and neoplasias that differ from those occurring in the general population by their high aggressiveness, unusual location, early tendency to generalization, frequent relapse, and short survival. The severe complications of AIDS, however, represent only the last phase in a prolonged course of progressive dysfunction and destruction of the immune system set in motion by the infection with the human immunodeficiency virus (HIV). While substantial progress was achieved in the ultrastructural identification and biochemical characterization of HIV, its mode of action in the causation of AIDS is not yet fully understood.

This article explores the main processes involved in the HIV infection and in its role in the origin of AIDS. It describes the phases of HIV infection, investigates the effects of HIV on the various components of the immune system, and analyzes the pathogenesis of the HIV-induced lymphadenopathies and encephalopathy, as well as the causes and mechanisms of AIDS-associated opportunistic infections and opportunistic neoplasias. The total failure of immune surveillance against a host of infectious and oncogenic agents, unprecedented in human pathology, is thus traced to the initial event of specific HIV infection of the CD4+ 
T-lymphocytes.

The broad spectrum of severe infections and neoplasias that constitute the expression of acquired immunodeficiency syndrome represents only one phase in the human infection with HIV. From the reporting of the first cases in 1981 to the present worldwide epidemic, the general attention has been focused on AIDS; however, it is the HIV infection that makes AIDS possible through its profound dysregulation and eventual destruction of the immune system. The epidemiology of the HIV infection has been frequently described as an iceberg in which the visible, smallest part is formed by the patients with AIDS, the middle by those with HIV lymphadenopathy or other HIV-related manifestations, and the largest, invisible part by the HIV-infected, yet asymptomatic persons (1).

In the few years since its discovery in 1983, HIV has been clearly visualized by electron microscopy; its structure, enzymes, and genetic material have been fully characterized; and its replicative process has been demonstrated in vitro (2-9). In contrast to the rapid progress achieved in the identification and biochemical characterization of HIV, its mode of action in the causation of AIDS is not yet fully understood. This paper will explore some of the processes involved in the HIV infection and in its progress to the terminal, severe complications of AIDS.

Phases of HIV Infection

The acute phase of HIV infection generally lasts several weeks. During this time substantial amounts of virus are produced, while those infected develop a nonspecific, flu-like syndrome that varies from almost nonnoticeable symptoms to a mononucleosis-like illness with fever, sore throat, malaise, lymphadenopathies, and sometimes cutaneous rashes (10).

The following chronic phase is the longest and most unpredictable. Its average length has been 7 yr, and the symptoms, often minimal, are sometimes marked by the persistence of generalized, mostly indolent lymphadenopathies. Some patients in this phase may be entirely symptom free in the presence of circulating anti-HIV antibodies. Others may revert to seronegativity. In both cases, however, reverse transcriptase activity and viral antigens could be demonstrated (11-13). The long, chronic, frequently silent period was interpreted as a state of occult infection in which virus replication may have been neutralized by antibody or entirely inhibited, resulting in different patterns of occult HIV infection (14). However, using the polymerase chain reaction method of amplification, the presence of HIV genetic material was demonstrated even in seronegative persons, while the identification of variations in the HIV nucleotide sequences indicated the continuous growth and mutation of the virus (15, 16). These findings resulted in a better understanding of the course of virus infection. Thus it appears that circulating infectious virus is constantly present and that viral replication occurs continuously, even during the chronic, clinically silent phase of the disease (16).

In the third phase of the disease, the symptoms of AIDS are full-blown, resulting in the appearance of opportunistic infections and neoplasias. The circulating virus is again apparent as its increasing titers correlate with the advancing disease (16-18). The progress of the disease from the initial HIV infection to the terminal episodes of AIDS has been described and classified into a 6-stage clinical system (19). The pathology of the various lesions of AIDS has been described and illustrated by various authors, and the surveillance definition of the syndrome has been formulated by the Centers for Disease Control (20, 21). In fact the progression from the acute first phase of the HIV infection to the complications' third phase of AIDS follows closely its cause: that is, the relentless decrease of CD4 lymphocytes (T4 cells). The correlation between the severity of symptoms and the total amount of T4 cells is well established and serves as the most reliable criterion of prognosis (22-24).

Since the progressive elimination of T4 cells is caused by HIV, it appears that the active replication and levels of viremia determine the phases of HIV infection. What controls the variations in virus replication and, consequently, the amount of T4 cells and progress of disease still remains undetermined (16).

HIV Effect on CD4 Lymphocytes

Cell-mediated immunity is mainly effected through the activity of the two major T-lymphocyte subpopulations: CD4 helper/inducer (T4) and CD8 cytotoxic/suppressor (T8) cells. HIV manifests a strong, exclusive tropism for the T4 cells, which are selectively infected by the virus (25). The basis for this characteristic affinity is the CD4 molecule on the surface of the T4 cells serving as specific receptor for the virus (25-27). In vitro infection of T4 cells by HIV can be blocked by monoclonal antibodies raised against CD4, and in vivo infection of T4 cells by HIV can be blocked by antibodies raised against CD4.
antibodies directed against specific epitopes on the CD4 molecule (26, 27). Similarly, when HIV is bound to T4 cells, the immunoprecipitation of the CD4 molecule results in the coprecipitation of gp120, the major envelope glycoprotein of HIV, and conversely the immunoprecipitation of gp120 coprecipitates the CD4 molecule (28).

Subsequent to HIV binding, viral entry and replication within T4 cells follow. While these initial phases have been well documented, the mode by which the infected cells are destroyed is not entirely clear (24, 29, 30). A substantial amount of T4 cells are presumably killed by the cytopathicity of the infecting virus; however, marked decreases in the population of T4 cells have been recorded even when only a modest amount of T4 cells in peripheral blood and lymph nodes showed signs of HIV infection or when populations of T4 cells bearing few CD4 markers on their surface were exposed to the virus (24, 29). To account for the apparent discrepancy between the paucity of HIV-infected T4 cells and their considerable decrease, other mechanisms for the loss of T4 cells were postulated. Formation of syncytia by fusion of HIV-infected cells observed in vitro was proposed as a mechanism for T4 cell depletion; however, in vivo, syncytial cells are only infrequently seen in lymph nodes and the brain (31, 32). The accumulation of unintegrated HIV DNA, known to by cytopathic in other RNA virus systems, has been also proposed as a mechanism for cell killing but not supported by experimental findings (29). The thymus shows premature involution in AIDS patients, which suggests possible inhibition in the production or maturation of T4 cells, thus contributing to their low counts during the HIV infection and AIDS (30).

Autoimmune mechanisms have also been implicated in the selective depletion of T4 cells when the presence of lymphocytotropic autoantibodies was demonstrated in HIV-infected and in AIDS patients (33–35). By testing a population of 200 AIDS patients for the presence of ALA, we found that 88% had significant levels of ALA directed selectively against T4 (helper) lymphocytes (>2 SD above the mean ALA level of 50 HIV-negative homosexual males) as compared with only 8% of a control group of patients with non-AIDS-related diseases (33).

In a prospective study designed to investigate the relationship between ALA and the progression of clinical disease, the levels of ALA were determined in 61 patients with ARC who were followed from 18 to 30 mo. During this interval 31 patients (67%) of those with significant elevation of ALA levels developed the complications of AIDS, while none of 15 patients without ALA elevation progressed to AIDS (36). The generation of autoantibodies directed against lymphocytes is not entirely unexpected in a syndrome characterized by broad immune deregulation. Indeed, in addition to antilymphocyte antibodies, a variety of autoantibodies directed against other cell types including platelets, granulocytes, and erythrocytes as well as against various protein antigens such as actin, tubulin, thyroglobulin, albumin, myosin, and DNA have been identified in patients with AIDS (37–41).

The T4 lymphocytes are not only quantitatively diminished as a result of the HIV infection, but also impaired in some of their specific functions even before their numbers have substantially fallen. Thus T4 cells of HIV-infected persons fail to show a proliferative response to the stimulation of specific antigens such as tetanus toxoid, influenza virus, CMV, Toxoplasma, Candida, and Cryptosporidium, which explains the frequent occurrence of these particular infections in patients with AIDS (30, 42, 43).

HIV Effect on CD8 Lymphocytes

The T4/T8 cell ratio, normally about 1, decreases steadily during the HIV infection, falling as low as 0.1 in the final phases of AIDS. Most of the decrease reflects the continuous depletion of the T4 cell pool; however, changes in the numbers of CD8 (T8) cells may also occur. HIV-seropositive persons that are still asymptomatic or present with the ARC were found to have elevated levels of T8 cells, particularly some subsets of these cytotoxic/suppressor cells (24). The expansion of the T8 cell population may represent a cytotoxic response to the replication of HIV and/or other pathogens (44). An additional stimulus for the proliferation of T8 cells may be the need to control the activation of B-cells which takes place at the same time (24). In the late stages of AIDS, however, the amount of T8 cells also declines, becoming very low in the terminal phases of AIDS (24, 33).

HIV Effect on B-Lymphocytes

The humoral immunity is also severely compromised as a result of multiple B-cell abnormalities in the HIV infection (24, 29, 30). There are strong B-cell activation, polyclonal proliferation, and hypergammaglobulinemia. Increased secretion of IgG, IgA, and IgD occurs in HIV-infected adults, while IgM hypergammaglobulinemia is prevalent in children (24, 45). Despite the high levels of immunoglobulins, the antibody responses to novel antigens are poor (29, 45). Moreover, in the absence of T4 helper cells, the B-cell response to mitogens remains significantly impaired (24, 30, 45). As a result of the severe B-cell dysregulation, severe pyogenic infections, particularly with Streptococcus pneumoniae and Haemophilus influenzae, occur in HIV-infected persons, particularly neonates and children (43, 46). The causes of B-cell activation and proliferation may be multiple, including a direct effect on B-cells by HIV, reactivation of other viruses such as EBV and CMV, impaired downregulation by T-cells, and abnormal lymphokine production by infected macrophages (30, 47). In addition to the defective response to recall antigens and the impaired function of B-cells, their activation during the HIV infection may be of pathogenic significance in the origin of AIDS-associated lymphomas (48–50). Thus the failure of T4 lymphocytes to exercise normal immune surveillance may favor the unrestricted proliferation of EBV-infected B-cells in the AIDS patients (48–50).

HIV Effect on The Mononuclear-Phagocyte System

Monocytes, macrophages, lymph node dendritic cells, pulmonary alveolar cells, and cutaneous Langerhans cells, the normal constituents of the mononuclear-phagocyte system, are all potential targets of HIV. The monocytes express membrane CD4 antigen and are therefore like the CD4+ T-lymphocytes (T4 cells), natural receptors for HIV. Virus antigen and particles have been identified on the surface and processes of monocytes, dendritic cells, and Langerhans cells (2, 3, 51–53). In addition, macrophages are able to internalize HIV after it is coated with antibodies (54). In contrast to the T4 cells, the infected monocytes and macrophages are not killed by HIV which is able to survive and replicate in their cytoplasm. Budding virus has been demonstrated inside vacuoles and the Golgi apparatus (52).

The involvement of monocytes/macrophages in the HIV infection has severe consequences. The binding of the CD4 monocyte receptors prevents further interactions with lymphocytes, thus abrogating the central role of monocytes/macro-
phages in the process of antigen presentation. The high incidence of infection with *Pneumocystis carinii* in AIDS patients may be related to the infection of pulmonary alveolar macrophages by HIV (29). The HIV encephalitis with its devastating effects is caused by the transportation of virus to the brain by the circulating monocytes. In the general circulation, HIV-infected monocytes and macrophages release interleukin 1 and cachectin (tumor necrosis factor), both strong pyrogens and catabolic agents, which fact probably explains the persistent fevers and the wasting effects of the disease, causing the terminal cachexia and the African Slim disease (55, 56). The infection of the monocyte/macrophage system by HIV is thus of utmost importance because it provides a permanent reservoir of virus and a means to ensure viral circulation and tissue reinfection.

**HIV-associated Lymphadenopathies**

PGL is a frequent manifestation of the HIV infection. A number of reports have described the histological changes which, although not unique to this disease, are sufficiently characteristic to have important diagnostic value when occurring in persons at risk for AIDS or in association with abnormal T4 cell counts (57–63). Three different histological patterns were recognized and shown to correlate with clinical stages of the disease by studies of sequential biopsies in the same patients and by long-term follow-up studies of patients with PGL (20, 64–67).

The type A histological pattern is characterized by greatly enlarged lymphoid follicles comprising hyperplastic germinal centers which show marked cytolyis, phagocytosis of nuclear debris by macrophages, and cellular regeneration with numerous cells in mitosis. There are also characteristic multinucleated giant cells, transformed monocytoid B-cells, infiltration of follicles by small mantle lymphocytes, and disruption of the dendritic cell network (20, 57). All these changes, single or combined, can be seen in other acute viral lymphadenitides. Immunological and ultramicroscopic studies of lymph nodes in the acute phase of PGL have confirmed their viral etiology by demonstrating the presence of HIV antigen and HIV particles in the affected follicles most often on and around the processes of the dendritic reticular cells (2, 3, 52, 53, 68, 69).

Type B pattern combines features of A and C patterns, probably representing a transitional stage, while type C pattern is characterized by advanced follicle atrophy, lymphocytic depletion, and abundant vascular proliferation (20, 67). The histological appearance of this late stage of chronic viral lymphadenitis closely resembles several other lymphadenopathies of unknown etiology such as Castleman’s lymphadenopathy, angioimmunoblastic lymphadenopathy and, to some extent, even Kaposi’s sarcoma of lymph nodes, which all have in common with the HIV lymphadenopathy a background of severe immune deficiency. In one study, the histopathology of 74 sequential lymph node biopsies in 30 patients with ARC or AIDS showed a temporal progression from lesions of follicular hyperplasia to lesions of lymphocytic depletion in correlation with the aggravation of clinical symptoms and the appearance of the opportunistic infections of AIDS (66). In a different study, 79 patients with HIV-related lymphadenopathies followed for intervals of up to 7.2 yr, the three histological patterns showed significant correlations with the progression from ARC to AIDS (67). In this study of 31 patients who had a type A pattern at the initial lymph node biopsy, 58% remained stationary and 42% progressed to AIDS, while of the 17 patients who initially had histological pattern C, only 6% remained stationary and 94% progressed to AIDS. During the follow-up, 32% of those with pattern A and 88% of those with pattern C died with median survival times of 54.4 and 8.4 mo, respectively (67). The pathogenetic significance of lymph node morphological changes is not yet fully understood; however, the histological patterns appear to correlate with the dysregulation of the immune system and with the clinical progression of disease, suggesting their usefulness as prognostic indicators.

**HIV-associated Encephalopathy**

The nervous system is a major target for both the HIV infection and the opportunistic infections and neoplasms of AIDS. One of the most common and severe forms of neurological involvement is subacute encephalopathy with progressive dementia. It is estimated that 10% of AIDS patients present first with neurological symptoms and that as many as 60% will eventually develop dementia (70). Early symptoms consisting of difficulties with concentration and memory as well as motor dysfunctions, such as incoordination and poor balance, may occur shortly after seroconversion before any other manifestations (71). In the later stages of the HIV infection, patients may develop the full syndrome of ADC characterized by severe cognitive, motor, and behavioral dysfunction (72). In such advanced stages, the brain decreases in size, showing enlarged ventricles and atrophic cerebral substance, changes that can be recognized on computerized tomography scans. The most affected are the subcortical structures including the central white matter and the deep gray structures including the basal ganglia, the thalamus, the brain stem, and the spinal cord with relative sparing of the cortex (71, 73).

Histologically, brains with ADC show randomly scattered small collections of multinucleated giant cells, macrophages, lymphocytes, and microglial cells located in areas of demyelination, frequently around blood vessels. The multinucleated giant cells are similar to those seen in the HIV lymphadenopathy and likewise of monocyte/macrophage origin (73–76). Electron microscopic examination of brain tissues shows typical retroviral particles budding from and associated with the plasma membranes of mononucleated or multinucleated macrophages (75, 76). Tissue sections from the cortex of brains with ADC examined by *in situ* hybridization showed that 15 to 70% of the multinucleated giant cells contained HIV RNA (76, 77). Thus it appears that monocytes and macrophages are the cells that, after becoming infected with HIV, constitute a permanent reservoir for the virus and facilitate its transport across the blood-brain barrier into the central nervous system. The major lesion of the cerebral tissues consists of demyelination which seems not to be produced by a direct viral effect but rather by the release of toxic monokines and proteolytic enzymes by the infected monocytes, macrophages, and giant cells (29).

**AIDS-associated Opportunistic Infections**

The most common causes of morbidity and mortality in HIV-infected patients are the opportunistic infections associated with AIDS. In autopsy studies of AIDS patients, opportunistic infections were the cause of death in 90% of cases (78, 79). The spectrum of pathogens is very broad including a large number and variety of viruses, bacteria, fungi, and protozoa (20). In most cases, the infections are caused by microorganisms normally controlled by cellular immunity which is failing in AIDS. However, a number of infections with bacteria normally con-
trolled by humoral immunity are also occurring, particularly in children, caused by the concomitant deficiency of the B-cells. The high susceptibility of AIDS patients for infections is determined by their immune deficiency and correlates directly with the decrease in the amount of T4 cells. The lower the T4 cell counts, the more frequent and severe were the opportunistic infections. Generally, until the amount of T4 cells falls below 250/mm³, AIDS patients do not show abnormal susceptibility to P. carinii, MAI, or CMV (80). The most common pathogens in AIDS are microorganisms that rarely if ever cause disseminated disease in normal, immune competent persons. Moreover, it appears that the spectrum of infections and their pathogenicity in AIDS differ even from those of other, non-AIDS immune deficiencies (80). MAI and Cryptosporidium, frequent causes of infection in AIDS, are found exceedingly rarely in association with other immune deficiencies, while toxoplasmosis and candidiasis are by far more common in patients with AIDS (80, 82, 83). The explanations for the characteristic constellation of infections in AIDS must be related to the particular dysregulation of the immune system in this disease, although the specific correlations are not yet understood. Most infections are the result not of recent exposure, but rather of the reactivation of remote primary infections not infrequently acquired in childhood (80). This appears to be the case, particularly with such ubiquitous infectious agents as Mycobacterium tuberculosis, Toxoplasma gondii, Histoplasma capsulatum, and P. carinii. In this respect, geographical location plays an important role as pathogens that are prevalent in certain areas tend also to be the common causes of opportunistic infections in AIDS patients residing in or originating from such areas. Examples are the higher incidence of tuberculosis in AIDS patients from Haiti, of histoplasmosis in AIDS patients from the Mississippi basin, and of coccidioidomycosis in AIDS patients from the southwestern United States (20, 80). A dominant feature of the opportunistic infections associated with AIDS is their high rate of recurrence, determined by the persistent and so far incurable immune deficiency. For this reason in many cases the treatment of infections in AIDS patients is bound to continue for life (80).

AIDS-associated Opportunistic Neoplasias

Not unlike infections, neoplasias are also more common in persons with immune deficiencies than in the normally immune competent general population (84). The risk of developing a malignant tumor is 4% for persons with genetic immunodeficiency, an increase of 10,000 times over the usual, and 6% in immunosuppressed recipients of renal transplants (85, 86). In AIDS, the frequent occurrence of neoplasms of particular types was noted from the beginning of the epidemic (87, 88). KS, NHL, and epithelial tumors of the anus; neoplasias also associated with other types of immune deficiencies, occur in AIDS patients with an incidence that far exceeds the one recorded in the general population (89–93).

Kaposi’s sarcoma, a neoplasm occurring in only 0.02% of the general population, affects 4.9% of renal transplant patients and is the malignancy most commonly associated with AIDS (94). Even within the AIDS populations KS shows a selective distribution related to risk groups occurring in 45% of homosexual but in only 4 to 8% of nonhomosexual males (95). Recently, a substantial decrease in the incidence of KS in AIDS homosexuals has been noted, possibly related to a parallel decrease in the rate of some opportunistic infections, particularly CMV (94). Investigations into the etiology of KS indicate a possible relation with the CMV infection, as virus particles of the herpes type have been seen in tissue cultures of KS, and DNA sequences of CMV, as well as CMV-related antigens, have been identified in biopsies of KS lesions (96).

Lymphoma, the most common tumor to occur in congenital immune deficiencies and in medically immunosuppressed patients, is also frequently seen as a complication of AIDS (97). The rapid increase in the incidence of NHL among AIDS patients was acknowledged by its inclusion in the Centers for Disease Control definition of AIDS (21). Lymphomas in AIDS are not only more common but also different in their clinicopathologic features from their counterparts in non-AIDS persons. In AIDS, NHLs exceed the incidence of HLs in contrast to their respective proportion in the general population, particularly in young adults where HL is more common. In a study of 104 cases of AIDS-associated lymphomas there were 93 cases of NHL and only 11 cases of HL (98). There is also a striking reversion in the proportion between NHL located in lymph nodes and NHL in extranodal locations. In the present series, there were 40 lymphomas in lymph nodes and 54 extranodally, a sharp contrast to the ratio commonly seen in non-AIDS lymphomas (98). Of these, 29 NHLs arose in the digestive tract, including the oral cavity and anus, locations otherwise rarely encountered. The central nervous system, involved in the general population in only 1 to 2% of lymphomas, is the site of NHL most often, the primary and only site in 11 to 42% of AIDS cases (90, 92). Histologically, lymphomas of high-grade type are predominant, which is reflected in the tendency to early dissemination and short survival of these neoplasias (90–92). The most common histological types of AIDS-associated NHLs are Burkitt’s and immunoblastic neoplasias known to be associated with a state of immune deficiency and possibly with a viral etiology. Burkitt’s lymphoma in African children is believed to be related to early infection with EBV in a population with severe immune deficiency caused by endemic malaria (48, 99, 100). The EBV-activated B-cells proliferating in the absence of T-cell surveillance may undergo mutations, genetic aberrations, and neoplasia. AIDS-lymphomas with very few exceptions all have been of B-cell phenotype (98, 101). They also showed chromosomal translocations similar to those in the African Burkitt’s lymphomas, particularly the characteristic t(8:14) (102). The translocation involves the c-myc gene locus on chromosome 8 and the immunoglobulin heavy chain on chromosome 14, resulting in an oncogene rearrangement not usually seen in non-Burkitt’s lymphomas (101). Using both filter and in situ hybridization techniques, EBV sequences were identified in the genome of AIDS-lymphoma cells (101, 103). In contrast, hybridization assays for the detection of HIV in lymphoma cells were negative, indicating a lack of oncogenicity for this virus (102).

Epithelial tumors of the anus, ranging from benign condylomas to carcinomas in situ or Bowen’s disease to squamous cell carcinomas, are occurring with unusual frequency in HIV-infected, homosexual males. HPV of different types has been regularly detected in such tumors by in situ hybridization and by immunohistochemical staining with type-specific monoclonal antibodies (93).

The study of neoplasms occurring in HIV-infected and AIDS individuals leads to the conclusion that they represent a characteristic group with many features similar to those of opportunistic infections (84). The tumors are specific for their association with immune deficiency, their incidence is unusually high, their manifestations are severe, they have a strong tendency for invasion and early dissemination, and they are resistant to treatment and prone to relapse. Most if not all appear to be
associated with viruses that are widely spread though largely innocuous in the general population but oncogenic in immune-deficient persons. Thus in the absence of immune surveillance innocuous in the general population but oncogenic in immune-associated with viruses that are widely spread though largely

In an unprecedented fashion in human pathology, what begins as a viral infection ends as a broad spectrum of severe opportunistic infections and neoplasia made possible by the long course of progressive dysfunction and eventual destruction of the immune system.

References


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