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Research Article

The Acquired Immunodeficiency Syndrome (AIDS)

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Introduction

In less than three years, a novel form of acquired immunodeficiency has been newly described, its epidemiology established, the characteristic immunopathology defined, and the etiologic agent identified. The acquired immunodeficiency syndrome, better known by its acronym AIDS,[1] is a spectrum of abnormalities ranging from the full-blown form in patients with opportunistic infections and certain bizarre malignancies to a more benign form in patients with lymphadenopathy and fever. All groups have a characteristic immunological abnormality that will be discussed below. AIDS has been recognized almost exclusively in certain "at risk" groups, so much so that the diagnosis is almost certainly excluded in patients from groups not "at risk." Over 70% of the cases have been reported in homosexually active males (1–3). The second largest group of patients have been intravenous drug abusers (4). The syndrome has been diagnosed in hemophiliacs receiving Factor VIII concentrates and in other recipients of blood products or whole blood (5–9). Gamma globulin (immune serum globulin) has not, however, been incriminated in the transmission of AIDS. Infants born to mothers in the aforementioned risk groups have developed the syndrome even when separated from their mothers at birth (10, 11).

AIDS has been diagnosed among Haitian immigrants in the United States and among individuals from Zaire who reside in Belgium and France (12, 13). This has led to the recognition of the fact that there is probably a large reservoir of AIDS, or at least its causative agent, in the Caribbean and in Central Africa. The pattern of spread of AIDS strongly incriminated a putative transmissible agent as the cause of the syndrome. The epidemiology of the disease resembles the spread of hepatitis B virus and suggested that blood or other body fluids were contaminated with a transmissible agent. In the past year, investigators at the Pasteur Institute, Paris, and the National Cancer Institute, Bethesda, MD, have identified a lymphocytotropic retrovirus in the tissues of AIDS victims and there is compelling evidence that this agent is the cause of AIDS (14, 15).

Clinical considerations

The outstanding clinical feature of AIDS is the occurrence of opportunistic infections in individuals who have no prior known cause of immunodeficiency. Susceptibility to opportunistic pathogens has long been recognized among patients with congenital T cell defects and among recipients of chemotherapeutic agents or irradiation that cause T cell depletion. Most prominent among these infections is pneumonia due to *Pneumocystis carinii* and oral thrush from *Candida albicans*. There has also been a high incidence of cytomegalovirus, atypical mycobacteria, cryptosporidium, and *Herpes simplex* virus. Central nervous system invasion by *Cryptococcus neoformans* and *Toxoplasma gondi* has also been reported with significant frequency in AIDS patients. Bizarre malignancies have been noted. An extremely rare endothelial tumor, Kaposi's sarcoma, formerly regarded as a curiosity in the elderly, has been the most persistently observed malignancy in AIDS patients (16). However, it has been known to have younger victims in sub-Sahara Africa (17). An etiologic nexus between the AIDS agent and Kaposi's sarcoma may prove to be as complex as that between Epstein-Barr virus and Burkitt's lymphoma. In any event, the mortality rate in patients with opportunistic infections with or without Kaposi's sarcoma is extremely high and survival from onset of the full-blown syndrome to death rarely exceeds a year or two.

A more mild version of the syndrome has been recognized among risk groups and has been called pre-AIDS or AIDS-related syndrome. It consists of persistent lymphadenopathy, night sweats, fever, and weight loss (18). Only a small proportion of patients, perhaps 10%, with the prodrome progress to the full-blown syndrome. Yet, the full-blown form of AIDS may occur without a prodromal stage.

The characteristic immunologic abnormality is in some degree common to these various groups of patients and has been observed in totally asymptomatic individuals in high risk groups (19).

Immunological considerations

Lymphopenia becomes progressively more pronounced as the syndrome progresses. The subset of T lymphocytes defined by monoclonal antibodies to T4 (or Leu 3) is depleted and the acquired, persistent quantitative and functional depression of T4 cells is the hallmark of full-blown AIDS. This subpopulation of lymphocytes was at first designated as the "helper" T cells because they are critical to in vitro B cell activation and maturation to antibody synthesis and secretion. However, the complexity of the immune response did not long permit such a neat distinction to persist. AIDS patients were found to be paradoxically hypergammaglobulinemic. In fact, in vitro spontaneous hyperactivity of B cells is yet another prominent feature of AIDS (20). The further development of monoclonal antibodies to define T cell subpopulations more precisely revealed that a true helper subpopulation of T4 cells was not

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1. *Abbreviations used in this paper:* AIDS, acquired immunodeficiency syndrome; HTLV, human T cell leukemia virus; MHC, major human histocompatibility complex.

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as perturbed in AIDS as another T4 subgroup designated T4+, Leu 8+, TQ1+, which is not responsible for the induction of B cell responses (21). In functional terms, the patients lose cutaneous delayed hypersensitivity reactions both to recall and to new antigens. In vitro lymphocyte proliferative responses to mitogens, antigens, and alloantigens are lost. T cell-mediated cytotoxicity is diminished. There is a failure of T cells in vitro to synthesize and release T cell growth factor or interleukin-2 (22, 23). *De novo* antibody responses to new antigens are lost although antibody titers to previously encountered antigens remain normal or elevated.

The lymph nodes early in the disease exhibit follicular hyperplasia and the germinal centers are infiltrated by T8 (or Leu 3) lymphocytes, the reciprocal subset of T4 cells; T8 cells become predominant in the T cell areas and plasma cell infiltration and disruption of the follicular dendritic reticulum cell structure precedes follicular involution (24). The mounting number of T8 cells and diminution in T4 cells cause an inversion of the normal T4:T8 ratio, that is usually 1.5 to 2.0, and this perturbation has been used as a diagnostic test for AIDS. The causative agent(s) appears to have a cytotropism for activated T4 cells (25). It seems likely but it has not been proven that the host defense mechanism is the attempt of the cytotoxic T8 cells to destroy the virus-infected T4 cells. It has more recently become clear that T4 and T8 cells have important reciprocal cognitive functions. T4 cells recognize antigen in the context of class II major histocompatibility complex (MHC) products (HLA-D) whereas T8 cells recognize antigen in the context of class I MHC products (HLA-A, B, C) (26, 27). Therein must reside the functional importance of the T4 and T8 antigens on T lymphocytes. The previously held view that these antigenic markers neatly divided "helper" from "suppressor" T cells is no longer tenable and this awareness clarifies many of the old paradoxes that used to befuddle attempts to explain inconsistencies in the interpretation of the immunopathology of AIDS.

There are a number of immunologic consequences of the aforementioned events in AIDS that remain to be explained. Down-regulation of Ia (MHC class II) antigens is observed in cells of monocyte lineage (28). Elevated levels of circulating immune complexes are found together with increased circulating antilymphocyte antibodies, soluble suppressor factors, acid-labile α-interferon, β_2 microglobulin, and α_1 thymosine (29–31). At present, to make an educated guess, it seems likely that these are all secondary events.

Etiologic considerations

As previously mentioned, two groups of investigators have identified a lymphocytotropic retrovirus from blood and node lymphocytes of patients with full-blown AIDS or of patients with the prodromal manifestations. The Pasteur group calls their agent LAV for lymphadenopathy virus whereas the Bethesda workers have designated the agent human T cell leukemia virus III (HTLV III) (14, 15). It is similar to but distinct from HTLV I and II. Seropositivity has been found in a very high proportion of all risk groups. It has been possible to propagate the virus in transformed human neoplastic T cells. There is some cross-reactivity of antibody to the envelope proteins of HTLV I and HTLV III and this probably caused confusion early on when some 40% of AIDS patients were found to have antibody to HTLV I. It seems that the development of successful therapeutic or vaccination strategies will now depend to a greater extent on our understanding of the cytopathic mechanisms of these agents and their effects on the immune response.

Relationship to other immunodeficiency diseases

Lymphocytotropic viruses have been known to cause immunodeficiency in animal models. A form of AIDS has been observed in macaque monkeys. Simian AIDS is characterized not only by opportunistic infections but is also different from the human form by the occurrence of profound neutropenia and lymphopenia and hypogammaglobulinemia. A type D lymphocytotropic retrovirus has been isolated from affected monkeys (32).

For many years, a lymphocytotropic retrovirus has been known to cause feline leukemia. The feline leukemia virus causes immunosuppression in cats and renders them exquisitely susceptible to opportunistic infections. This susceptibility in cats is a more common outcome from feline leukemia virus infection than leukemia itself (33).

Measles virus in man is known to infect the cellular elements of the immune system. Anergy is a well-known complication of measles infection but the mechanism of this anergy is not well understood. Infectious mononucleosis has been better studied in this regard. Epstein-Barr virus gives rise to a period of self-limited immunosuppression by activation of the T cell suppressor network (34). It is not clear what terminates this temporary immunodeficiency associated with infectious mononucleosis.

Among the primary immunodeficiencies, AIDS most resembles the defect observed in purine nucleoside phosphorylase deficiency (35). This defect is inherited as an autosomal recessive phenomenon. Because of this deficiency, there is a failure in affected children to convert inosine or guanosine to hypoxanthine with a consequent accumulation of the metabolites, deoxyguanosine and guanosine triphosphate. Deoxyguanosine triphosphate is known to inhibit the enzyme ribonucleotide reductase and this is toxic to dividing cells (36). Children with nucleoside phosphorylase deficiency exhibit undue susceptibility to opportunistic infection. They are lymphopenic and do not mount delayed hypersensitivity reactions. However, they have normal immunoglobulin levels. Affected infants, like AIDS patients, tend to have an increased incidence of autoimmune disease and drug hypersensitivity. It seems likely that T helper cells divide less frequently than other T cells and are therefore less subject to the toxic effects of deoxyguanosine.

An elevation of T suppressor cells is known to occur in many immunodeficiency diseases and appears to be secondary to recurrent infections (37). Antigen overload in experimental animals and man has been shown to suppress immune responses and to down-regulate Ia antigen expression on monocytes and perhaps other cellular components of the immune system (38). These observations lead to an important question about susceptibility to AIDS. Is there a necessary precondition for the development of AIDS? There is evidence that multiple infections or antigen overload characterize all the risk groups for AIDS. The number of proved AIDS cases in "normal" individuals that have resulted from blood transfusions is miniscule in comparison to the probable number of units of infected

blood that have been transfused. The answer to this important question may be obtained from further epidemiologic and immunologic studies.

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