Morphological Alterations in the Lymphoreticular System in Acquired Immunodeficiency Syndrome

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ABSTRACT

Acquired immunodeficiency syndrome (AIDS) manifests a profound deficiency in cellular and humoral immunity causing opportunistic infections with high mortality. Intensive searching for accurate diagnosis, effective treatment, and reliable preventions are in progress. Diagnostic findings include lymphocytopenia, decreased T-helper/T-suppressor ratio and antibodies against human T-lymphotropic retrovirus-III. Specific morphological markers for the diagnosis of AIDS are not yet available at this time. Consistent findings in the lymphoreticular system include a reactive hyperplasia in the onset to lymphocyte depletion in its advance stage. The frequently mentioned ultrastructural changes in lymphoreticular cells are tubulo-reticular structures, test tube and ring-shaped forms, multi-vesicular and virus-like particles. These are, however, nonspecific for the diagnosis of AIDS.

Introduction

In the past four years the acquired immunodeficiency syndrome, better known as AIDS, has become the most notorious disease in the world, challenging the health profession for the development of diagnosis, prevention, and effective treatment. Pertinent manifestations of AIDS include the unusual occurrence of Kaposi’s sarcoma, pneumocystis carinii pneumonia and other opportunistic infections in previously healthy young men.18,21,27,28 Subsequently, it was found that this syndrome is highly frequent in homosexual men, accounting for 71 percent of AIDS cases and intravenous drug abusers accounting for some 17 percent. Other groups with increased risk are Haitians, hemophiliacs receiving factor VIII concentrate, transfusion recipients, and infants born to mothers from groups at high risk.21 The possible involvement of human T-lymphotropic retroviruses—III(HTLV–III)25,33,35 in the causation of AIDS has become a focus of enormous attention because of the potential of a rapid blood test for the screening of blood as well as the development of a vaccine against HTLV–III.

In spite of an intensive investigation of AIDS, relatively little has been learned regarding the specific structural changes
MORPHOLOGICAL ALTERATIONS IN LYMPHORETICULAR SYSTEM IN AIDS

Lymph node enlargement is a fairly consistent finding of AIDS which is seen in three histologic patterns. The first pattern is one of exuberant follicular, paracortical, and focal sinusoidal hyperplasia. A second pattern seen is paracortical hyperplasia with small hypocellular and sometimes hyalinized follicles. In a third pattern, the lymph nodes are lymphocyte depleted giving an accentuated appearance to the fibrovascular elements resembling an irregular proliferation of small vessels. Additionally there are numerous tingible body macrophages scattered evenly throughout the germinal centers which produce a starry sky pattern or moth-eaten appearance. Nuclear debris is strewn about the germinal centers with frequent mitoses and aggregates of clear cells. These clear cells are larger than immunoblasts and exhibit fairly abundant strikingly clear cytoplasm with prominent cellular borders and rounded

Gross and Light Microscopic Findings

LYMPH NODES

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Figure 1. Lymph node with loss of germinal centers and marked lymphocyte depletion. × 100.

Figure 2. Higher magnification of figure 1 showing vascular proliferation. × 200.
nuclei with inconspicuous nucleoli.\textsuperscript{15} These are characteristically located around blood vessels, fibrosepta and the peripheral lymphocyte mantles of the lymphoid follicles.

There is almost universal presence of polymorphonuclear leukocytes in the sinuses of lymph nodes. They are also found in relation to necrotic cells and around the clear cells.\textsuperscript{15} It is noteworthy that many autopsy studies show marked depletion of cortical and paracortical lymphoid elements with a variable plasmacytosis. The changes seen perhaps represent a dynamic process encompassing a spectrum ranging from hyperplasia in the early stages of the disease to atrophy in latter stages. Other changes reported include granulomatous lymphadenitis\textsuperscript{2,12,37} destructive cytomegalovirus lymphadenitis,\textsuperscript{15,31} cryptococcal lymphadenitis,\textsuperscript{31} Kaposi's sarcoma,\textsuperscript{31} high grade lymphoma,\textsuperscript{3,4,38} and erythrophagocytophthosis.\textsuperscript{31} Immunohistochemical study reveals the reduction of ratios of T-helper/T-suppressor-cytotoxic in lymph nodes in AIDS patients. It is important to know that this decrease precedes the same changes in peripheral blood.\textsuperscript{30}

**Spleen**

The spleen is consistently enlarged and congested. Germinal centers are atrophic with absence of B-cell zones. There are changes ranging from mild depletion to virtual absence of lymphoid elements with scarring, fibrosis and diminished T-cell zones. Consistently, the spleen is one of the most commonly affected organs in systemic disease.\textsuperscript{31}

**Thymus**

The thymus exhibits almost complete...
absence of lymphoid elements with paucity of Hassall's corpuscles which in some cases are hardly identifiable. Others may show focal calcification.31

**Bone Marrow**

Non-paratrabeucular lymphohistocytic infiltrations consisting of irregular small lymphocytes were observed in approximately one third of all AIDS tissues studied.26 Lymphoid aggregates were found in 15 percent of the AIDS bone marrows.22 These are composed of heterogeneous populations of lymphocytes variable in shape with some having elongated nuclei; others are transformed lymphocytes. They usually have a paratrabeucular location.8 Plasmacytosis and dilated vascular channels with focally prominent arborizing blood vessels were noted in 25 percent of cases. Small granulomata are occasionally seen and may exhibit fungi or mycobacteria on special staining.

**Peripheral Blood**

The peripheral blood cell findings are rather non-specific. However, there is usually a mild anemia and marked lymphocytopenia with some atypical lymphocytes and relative monocytosis. There are no identifiable specific light microscopic features in lymphocytes of AIDS patients.

The total T and B cell ratios are within normal limits. Severe depletion of helper T-cells and relative or absolute increase of suppressor T-cells causing the reduction of ratios of helper/suppressor T-lymphocytes is also seen.20,24 The responses of lymphocytes to mitogens and specific antigens are often depressed, and defective activity of natural killer cells is commonly noted.

Based on antibody levels to pneumococcal polysaccharide, before and after immunization, it is understood that in addition to T-cell immunodeficiency AIDS patients also suffer from B-cell immunodeficiency.1,20 It is also recognized by serologic methods that positive IgG antibodies to HTLV-III were demonstrated in AIDS with 60 percent to 93 percent prevalence.32

**Ultrastructural Findings**

Several ultrastructural findings in lymphocytes of lymph nodes and peripheral blood of AIDS patients have recently been observed. Among these are tubuloreticular inclusions, vesicular rosettes, test tube and ring-shaped forms, multivesicular bodies, grouped vesicles, and viral particles. It is our experience that the lymphocytes in buffy coat specimen from the peripheral blood, which is usu-
ally readily available on most patients, is ideal for study.

Tubuloreticular inclusions (TRI), observed as early as 1968, are abnormal subcellular organelles arising within the subsecretory apparatus. They are seen in two forms depending upon the plane of section. First is a compact reticular pattern characterized by deeply osmiophilic profiles measuring up to two micrometers in maximum dimension. Cross-sections of tubular components located within cisternae of rough endoplasmic reticulum are sometimes surrounded by smooth endoplasmic reticulum measuring 20 to 30 nm in diameter. A second pattern is distinctly tubular characterized by multiple paranuclear profiles of loosely intertwined tubuli. Tubuloreticular inclusions are observed exclusively in mononuclear cells. In addition to AIDS, TRI are also seen in patients with systemic lupus erythematosus (SLE), herpes encephalitis, and viral hepatitis. The reported percentage for the identification of TRI in AIDS ranges from 21 to 80 percent.

Vesicular rosettes (VR) are unusual cytoplasmic bodies composed of multiple distinct 30 to 60 nm vesicles radially clustered around an ill-defined electron-dense core often seen in association with Golgi apparatus. They are devoid of any surrounding membrane and are not associated with the Golgi complex or any other organelle. The expected percentage of the identification of VR in AIDS ranges from 21 to 80 percent.

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Test tube and ring-shaped forms consist of electron opaque material included between two unit membranes and measure approximately 200 nm in diameter. These were first described in livers of chimpanzees infected with non-A and non-B hepatitis. The test tube and ring-shaped form is seen in 40 percent of AIDS patient’s lymphocytes.

Multivesicular bodies are membrane bound vacuoles containing small vesicles measuring 20 to 80 nm. They are surrounded concentrically by small vesicles which may arise from the Golgi apparatus and might alternatively become central vesicles. Multivesicular bodies are seen in 20 percent of AIDS patient lymphocytes. However, it is important to point out that multivesicular bodies are more frequently seen in reactive lymph nodes.

Grouped vesicles are radially arranged vesicles with an ill-defined electron-dense core often seen in association with Golgi apparatus. They also exhibit variable size and arrangement. Their significance lies in that they may be mistaken for vesicular rosettes.

The HTLV-III viruses have been described in cell cultured specimens of AIDS patients. The HTLV-III virus possesses a cylindrically shaped core with a diameter of 100 to 120 nm which buds from the cell membrane in high numbers. Another form of these retroviruses shows immature particles with dense crescentic budding at the center surface and mature particles with a small dense eccentric core in the extracellular spaces.

Virus-like particles have been described in AIDS specimens. However, these particles are also noticed in non-AIDS patients. The significance of these virus-like particles still remains unclear.

Summary

Consistent findings in the lymphoreticular system in light microscopy include reactive hyperplasia in the onset to lymphocyte depletion in its terminal stage. This represents a spectrum of morphologic change involving a process about which much is yet to be learned. The lymphocyte functions indicate both T- as well as B-lymphocyte immunodeficiencies. The reduction of the helper/suppressor T lymphocytes still serves as
one of the most useful diagnostic markers.

While there appears to be an association between the presence of tubuloreticular structures and test tube and ring-shaped forms with AIDS, the diagnostic significance of ultrastructural multivesicular and virus-like particles is not known at this time. Additionally these are known to occur in several other diseases involving immune dysfunction or viral disease.10

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References


