Lymph Node Pathology of Acquired Immunodeficiency Syndrome (AIDS)*

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ABSTRACT

There has been a recent notable increase in the number of patients in the United States seropositive for the human immunodeficiency virus (HIV) and also an increase in the number of otherwise healthy homosexuals with persistent generalized lymphadenopathy (PGL). Lymphoid tissue appears to be a favorite target for the initial viral infection, subsequent opportunistic infections, and associated neoplasms. Therefore, evaluation of PGL is important in understanding the nature of the disease.

Biopsies of the acquired immunodeficiency syndrome (AIDS) lymph nodes show a spectrum of abnormal lymphoid proliferations, eventual lymphoid depletion, Kaposi's sarcoma, and malignant lymphoma. Although the individual features of AIDS-related lymphadenopathy may not be specific, the constellation of histologic, immunologic, ultrastructural, and fine needle aspiration findings is characteristic.

Introduction

Ever since the introduction of the acquired immunodeficiency syndrome (AIDS) reported in 1981 and the widespread application of enzyme-linked immunosorbent assay (ELISA) as the screening test and the Western blot (WB) as the confirmatory test to detect antibody against human immunodeficiency virus (HIV) in the past five years, there has been a rapid increase in the number of patients in many countries, especially the United States. There has also been an increasing number of otherwise healthy homosexuals with persistent generalized lymphadenopathy (PGL) characterized by the presence of enlarged lymph nodes in at least two extrainguinal sites for longer than three month period. Since the core antigens of retrovirus HIV have been sought in lymph nodes from patients with PGL, the PGL has been recognized as one of the AIDS-related conditions (ARC). Lymphoid tissue is a favorite target in the AIDS as being affected by the initial
virus infection, by the subsequent opportunistic infections, and by neoplasias. The evaluation of lymph node findings of PGL has been another approach to diagnosis and to the understanding the nature of the disease.\textsuperscript{22}

**Histopathology**

Many studies about PGL and AIDS lymph node histologic findings have been conducted, and results have been reported.\textsuperscript{6,9,17,22,25} Turner et al used a quantitative classification to evaluate serial lymph node biopsies in 20 homosexual men with PGL.\textsuperscript{25} The histology was classified based on the percentage of involuted follicles (table I). Involuted follicles were defined as either hyalinized or abnormally small. In a median follow-up interval of 19 months, Turner and co-workers found that ten patients had progression from one histologic subtype to another (50 percent). Only one of the patients had developed AIDS (five percent). It was concluded that subtypes of PGL were not stable in time, and progressive lymph node histopathologic subtypes did not correlate with the clinical course over a short time interval.

In the study by Stanley and Frizzera,\textsuperscript{22} the most common histologic pattern observed in PGL associated with AIDS was florid hyperplasia or germinal centers characterized by large and irregular follicles, mantle zone effacement, follicular lysis, hemorrhage, granuloma formation, and focal sinusoidal monocytoid cell hyperplasia. These morphologic features, however, occurred in a variety of other disorders. Without immunologic, immunohistologic, and clinical findings, these features could not be used as a definitive diagnosis of AIDS.\textsuperscript{22}

O'Murchadha et al reported that the histologic features of hyperplastic lymphadenopathy in AIDS-related complex (ARC) were nonspecific.\textsuperscript{17} Follicular hyperplasia was the most common histologic findings in lymph nodes from patients and PGL. Two sets of lymph node biopsy specimens from ARC and non-ARC groups were compared. It was concluded that there was no statistically significant difference between the two groups for histologic features such as irregularity of follicles, burnt-out follicles (lymphocyte depleted with fibrosis), sinus monocytoid cells, marked plasma cytosis, and the toxoplasmosis triad consisting of follicular hyperplasia, focal proliferation of transformed "histioid" B cells and scattered focal accumulations of small numbers of epithelioid-type macrophages not forming well defined granulomas.\textsuperscript{17,26} Ewing et al studied lymph nodes of patients symptomatically infected with HIV.\textsuperscript{6} The histologic features were classified into three patterns. The type I pattern featured follicular and paracortical hyperplasia. The type II pat-

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**TABLE I**

Classification of Generalized Lymphadenopathy

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Prominent Features</th>
<th>Percentage of Involuted Follicles</th>
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<tbody>
<tr>
<td>Follicular hyperplasia</td>
<td>Large, irregular follicles; aggregates of monocytoid B-cells; variable follicle disruption</td>
<td>0-25</td>
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<tr>
<td>Mixed follicular hyperplasia and involution</td>
<td>Variable follicle size, thin mantle zones, increased interfollicular areas compared to follicular hyperplasia</td>
<td>26-50</td>
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<tr>
<td>Follicular involution</td>
<td>Predominantly small, widely spaced follicles; relatively increased interfollicular areas with plasma cells</td>
<td>51-100</td>
</tr>
<tr>
<td>Lymphocyte depletion</td>
<td>Hypocellular appearance with few small or hyalinized follicles; predominant plasma cells, immunoblasts, and small vessels</td>
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tern showed diffuse lymphoid hyperplasia but loss of germinal centers. The type III pattern exhibited lymphocytic depletion and represented the end-stage lymph node seen in fatal AIDS. Progression through these three types took place in one direction only as from type I to type III.6

Ultrastructure

Two types of cytomembranous inclusions found in AIDS and ARC conditions were tubuloreticular inclusions (TRI) and cylindrical confronting cisternae (CCC). Studies indicated that the occurrence of TRI in AIDS, systemic lupus erythematosis (SLE), or viral infections was directly related to endogenous systemic or local elevations of type 1 interferons.12 The CCC could be seen in a variety of diseases including multiple sclerosis, adult T-cell leukemia (ATL), AIDS, malignancies, SLE, and chronic active hepatitis undergoing recombinant interferon alfa treatment. In AIDS, CCC frequently coexisted with TRI. Although the appearance of TRI and CCI was thought to indicate disease progression, to use TRI and CCI as “ultrastructural markers” remained to be investigated.12

Onerheim et al studied lymph nodes from nine patients with PGL, two patients with AIDS, and seven controls by electron microscopy. They concluded that there are no pathognomonic ultrastructural markers of AIDS or PGL, but tubuloreticular structures (TRS) are characteristic of both syndromes.18

Immunohistology

Numerous studies about immunohistologic findings in lymph nodes of patients with PGL and AIDS have been reported.2,3,15,19,21,24,28 Many have described the T-cell subset alterations in AIDS and PGL, as compared with non-AIDS group and peripheral blood findings.

Biberfeld et al studied T-cell subsets of lymph nodes from 43 homosexual men with PGL and 10 AIDS patients.28 Their observations showed consistently higher T4/T8 ratios in these lymph nodes as compared in the blood. However, among the PGL patients, T4/T8 lymph node ratios did not always correlate with the degree of follicular involution as findings in AIDS cases.

Modlin et al used monoclonal antibodies to study T-cell subsets in blood by cytofluorometry and in frozen sections of nodes by immunoperoxidase techniques.14 The homosexuals with Kaposi’s sarcoma had a T3/T4 ratio in blood of 0.7; the homosexuals with PGL had a ratio of 0.6 compared with controls of 2.1; the homosexuals with PGL had a ratio of 0.7 in the interfollicular areas of nodes; the homosexuals with Kaposi’s sarcoma 0.9 compared with control patients with a ratio of 3.0 (table II).

Schurmann et al reported that changes in blood lymphocytes do not exactly correlate with those in the lymph node.21 The disturbances in T4/T8 ratio were less pronounced in the lymph nodes than in blood. Turner et al suggested progressive severity of immunologic abnormalities in some patients with PGL syndrome.24 The immunohistologic findings

<table>
<thead>
<tr>
<th></th>
<th>Blood</th>
<th>Follicular Center</th>
<th>Mantle</th>
<th>Inter-Follicular T Zone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Controls</td>
<td>2.1±0.3 (1.8-2.4)</td>
<td>38±16 (4.0-50.0)</td>
<td>4.3±2.4 (1.0-8.0)</td>
<td>3.0±1.2 (1.8-5.0)</td>
</tr>
<tr>
<td>Homosexuals</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>with lymphadenopathy</td>
<td>1.5±0.6 (0.5-2.0)</td>
<td>0.9±0.3 (0.5-1.5)</td>
<td>3.0±1.2 (0.4-1.3)</td>
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<tr>
<td>Homosexuals</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>with Kaposi's sarcoma</td>
<td>0.7±0.3 (0.5-3.0)</td>
<td>0.8±0.3 (0.4-1.3)</td>
<td>0.9±0.3 (0.5-1.3)</td>
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correlated with peripheral blood findings
that showed progressively decreased
T4/T8 ratio in most of their patients with
PGL. However, none of their eight
patients developed opportunistic infec­
tions, Kaposi's sarcoma, or lymphoma.

Fine Needle Aspirate

The performance of frozen sections in
lymph nodes of patients who are in the
high risk categories for AIDS and who
have had PGL is not indicated because of
difficulties in interpreting the sections
and in decontaminating the cryostat. A
fine needle aspiration (FNA) is safe and
will not destroy the lymph node archi­
tecture.7 It is currently gaining accept­
tance as a rapid, minimally painful, and
relatively risk-free method. Bottles et al
did 121 FNA of lymph nodes from 113
men who were followed in the AIDS
outpatient clinic of the San Francisco
General Hospital. The cytologic diag­
noses were 60 (50 percent) hyperplasias,
24 (20 percent) non-Hodgkin's lymph­
omas, 21 (17 percent) mycobacterial
infections, 12 (10 percent) Kaposi's sar­
comas (KS), one Hodgkin's disease, one
giant cell carcinoma, and one squamous
cell carcinoma. No false positive results
but five false negative results occurred in
patients with hyperplasia on FNA.9 In
these five patients, subsequent histo­
logic examinations revealed three cases
of Hodgkin's disease, one case of non-
Hodgkin's lymphoma, and one case of
KS. The reasons for false negative results
were sampling errors in lymph nodes
with focal disease and sampling in be­
nign lymph nodes.

Hales et al reviewed 15 cases of KS
diagnosed by FNA. All patients were
homosexual males, and 13 had diagnosis of
AIDS. The aspirates were obtained from
enlarged lymph nodes (five cases),
soft tissue masses (two cases), oral cavity
lesions (seven cases), and abdominal
mass (one case). The most characteristic
cytological findings were intact tissue
fragments composed of overlapping
spindle cells with nuclear distortion and
ill-defined cytoplasmic borders. Smaller
groups of loosely cohesive spindle­
shaped cells and individual spindle cells
with cytoplasm were also helpful fea­
tures.8 Several potential pitfalls must be
considered before the diagnosis of KS
can be made by FNA. The differential
diagnosis of KS on FNA includes granu­
lation tissue, malignant fibrous histo­
toma, angiosarcoma, neurofibrosarcoma,
leiomyosarcoma, fibrosarcoma, synovial
sarcoma, and embryonal rhabdomyosar­
coma.8

Neoplasia

Certain neoplasias are associated with
AIDS.1,5,10,11,13,16 Ahmed et al reviewed
the occurrence of lymphomas in popula­
tions at high risk for AIDS including
prisoners from the state of New York and
non-prisoner intravenous drug abusers
(IVDA). Twenty-one prisoners and four
non-prisoner IVDA were found with
lymphoma. They were classified as 13
diffuse histiocytic, five Hodgkin's, four
Burkitt's, two diffuse mixed histiocytic,
and one diffuse poorly differentiated
lymphocytic lymphoma.1 The observed
number of prisoners with non-Hodgkin's
lymphoma (11) diagnosed between Jan­
uary 1, 1981 and December 12, 1984 is
significantly greater than the expected
number (2.28) based on age adjusted
incidence rates for the U.S. population
(P < 0.001).1 Although immune defi­
ciency states unrelated to AIDS are well
known to be associated with an increased
frequency of non-Hodgkin's lymphoma,
Ahmed and co-workers concluded that
non-Hodgkin's lymphoma is frequently a
manifestation of AIDS among IVDA and
is the most common malignancy seen in
IVDA with AIDS.1

Jaffe et al reported that the most com­
mon neoplasm in AIDS patients other
than KS is non-Hodgkin's lymphoma which is typically high-grade diffuse B-cell neoplasms of the undifferentiated (small noncleaved cell) (Burkitt's and non-Burkitt's) or large noncleaved cell types. A prevalence of advanced stage and high grade Hodgkin's disease diagnosed in AIDS population was also noted, although Hodgkin's disease is comparatively rarer than non-Hodgkin's lymphoma. Nasr et al reported a case of pulmonary T-cell lymphoma in an AIDS patient. It was large cell, immunoblastic category by the working formulation and had no association with manifestations of human T-lymphotropic virus (HTLV-I or II).

Summary

Most studies about histology, ultrastructure, immunohistology, fine needle aspiration, and neoplasia of AIDS lymph node which were reviewed by the current authors have similar results. The conclusions of these studies are as follows:

1. Although PGL has been recognized as one of the ARC, the histologic features are nonspecific and cannot be used as a definitive diagnosis without immunologic, immunohistologic, and clinical findings.

2. The correlation between progression of lymph node histopathologic subtypes and the clinical course over a long period of time interval remains to be investigated.

3. The ultrastructural findings of AIDS are nonspecific. The use of these findings as "ultrastructural markers" needs to be investigated.

4. Although most studies showed the disturbance in T4/T8 ratio is less pronounced in lymph node than in peripheral blood from AIDS cases, there is progressive severity of immunologic abnormalities.

5. Fine needle aspiration is a safe, rapid, and minimally painful and relatively risk-free method to investigate PGL. There are, however, several potential pitfalls to be considered before the diagnosis of KS.

6. Non-Hodgkin's lymphoma is the most common malignancy associated with AIDS besides KS. These lymphomas are mostly B-cell malignancies with one reported T-cell lymphoma. Other reported associated hematologic malignancies include Hodgkin's lymphoma, leukemia, and multiple myeloma.

Up to the present time, the definitive diagnosis of AIDS lymph node is still based on detection of HIV antibody. The evaluation of AIDS lymph node findings enable us to understand the nature and the progression of the disease.

References


8. Hales, M., Bottles, K., Miller, T., Donegan, E., and Ljung, B. M.: Diagnosis of


