Systemic Lymphadenopathic Histology in Human Immunodeficiency Virus-1–Seropositive Drug Addicts Without Apparent Acquired Immunodeficiency Syndrome

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We examined lymph nodes from multiple sites in 50 individuals infected with human immunodeficiency virus (HIV-1) who died accidentally of drug overdoses and in whom there was no evidence of opportunistic infection. The size, histologic pattern, presence of Warthin-Finkeldey–type giant cells, and estimation of CD4 cell count of these lymph nodes were compared with those of 13 seronegative drug addicts (controls). Lymph nodes from seropositive individuals were slightly but significantly larger than those of controls. Lymph nodes from seropositive cases were much more likely to contain secondary follicles (90%) than were those from controls (20%). Unlike follicles in control nodes, most secondary follicles in the seropositive cases were in various stages of fragmentation and involution. As follicular changes progressed, there was a decrease in CD4 cells and an increase in intrafollicular and paracortical plasma cells. Plasmacytosis was much more prevalent in lymph nodes from seropositive individuals than in controls. Warthin-Finkeldey–type giant cells were present in at least one node in 29 of 50 seropositive cases, were most numerous in those showing follicular hyperplasia with fragmentation (45% of cases), and were especially numerous in Peyer's patches (61% of cases). There was generally good concordance of HIV-1–associated follicular morphology among diverse lymph node groups. There is prolonged generalized, mild hyperplastic lymphadenopathy with frequent syncytial cells in intravenous drug addicts with asymptomatic HIV-1 infection. HUM PATHOL 25:248–256. Copyright © 1994 by W.B. Saunders Company

Histopathologic studies of lymph nodes removed from human immunodeficiency virus (HIV-1)-infected patients have been published since the discovery of the acquired immunodeficiency syndrome (AIDS)[1] and have concentrated on the histologic features of AIDS-related lymphadenopathy (AIDS-related complex/progressive generalized lymphadenopathy).[2-4] From these and subsequent data it has become clear that there are stages of lymph node changes.[5] These progress from follicular hyperplasia, characterized by large crowded follicles with an increase in the follicular dendritic cell network, to follicular involution, characterized by scarred atretic follicles and the disappearance of the follicular dendritic network. In end-stage lymph nodes there is a depletion of lymphocytes with a diffuse immunoblastic proliferation and effacement of the lymph node architecture.

The lymphadenopathic histology of HIV-1 disease lacks specificity for the diagnosis of HIV infection.[6] However, histopathologic staging of patients with known HIV-1 disease has potential value[7-10] and there is a decrease in the number of CD4-positive cells as the histopathologic stage progresses.[11] A correlation between clinical stage and histopathologic stage has been shown,[12] although the validity of this correlation has been questioned.[13]

Lacking in previous descriptions of HIV lymphadenopathy is a systematic examination of simultaneously sampled lymph nodes from multiple anatomic sites. Can lymphadenopathic features in a single lymph node biopsy be taken as representative of the morbid anatomy of the entire body's lymphoid organs? Furthermore, how does the presence of syncytial cells resembling Warthin-Finkeldey (WF) giant cells correlate with various histopathologic stages of HIV lymphadenopathy?

The purpose of this study was to provide data concerning the gross and microscopic morbid anatomy of diverse solid lymphoid organs in a large number of HIV-1–seropositive individuals without evidence of opportunistic infections. The concordance of histologic stage among various lymph node groups in a given individual, the number of OPD-4–positive (CD-4–positive) cells in each histologic stage, and the prevalence of WF-type giant cells were investigated.

MATERIALS AND METHODS

Case Selection

Sera from cases of unexpected death among intravenous drug abusers in the state of Maryland were screened for the

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TABLE 1. Mean Size of Lymph Nodes* and Presence of Warthin-Finkeldey Giant Cells by Lymph Node Pattern

	n	Percentage of Total Cases	Size (mm) (±SD)	No. of Cases With WF Giant Cells
Seropositive cases				
FH-FF	34	14.6	14.2 ± 4.3	6 (18%)
FH + FF	87	37.3	15.6 ± 4.3	42 (45%)
FI	87	37.3	14.5 ± 4.9	14 (19%)
LD	20	8.6	12.3 ± 3.8	3 (18%)
Sinus histiocytosis	5	2.2	10.3 ± 3.1	0
Seronegative cases				
Paracortical hyperplasia	15	31.3	11.0 ± 3.9	0
Follicular hyperplasia	11	22.9	11.3 ± 4.1	0
Sinus histiocytosis	22	45.8	9.3 ± 4.9	0

* Size was determined by measuring the greatest diameter of each node before processing.

presence of HIV-1 antibodies with a rapid ELISA kit (Genetic Systems Corporation, Redmond, WA) and were confirmed by Western blot testing performed at the Department of Health and Mental Hygiene, State of Maryland. Thirteen consecutive seronegative drug abusers and 50 consecutive seropositive cases were subjected to complete autopsies, including gross and histologic examination of internal organs and toxicologic analysis. The largest lymph nodes from the axillary, supraclavicular, mediastinal, inguinal, and mesenteric regions were measured along the long axis, bisected longitudinally, and routinely processed. Cases known to have AIDS and gross or microscopic evidence of opportunistic infection of the viscera or lymph nodes were excluded from the study. In a subset of cases tissues from Peyer's patches (n = 18), tonsil (n = 28), and spleen (n = 33) also were sampled.

Immunohistochemistry

The avidin-biotin complex method was applied to deparaffinized sections of tissues from all cases. The following antibodies were purchased from Dako Corporation (Indianapolis, IN): CD35 (1:20 dilution), OPD4 (1:50 dilution), and p24 (1:200 dilution). For CD35 and p24 tissue sections were predigested with protease K at 37°C (0.1 mg/mL) for 20 minutes (Sigma Chemical Co, St Louis, MO).

To attempt phenotyping of WF-type giant cells, select lymph nodes showing these cells were stained with S-100 protein (Dako; 1:600 dilution with digestion), QBend (Serotec, Indianapolis, IN; 1:150 dilution), factor-VIII–related antigen (Dako; 1:600 dilution), CD3 (Dako; 1:250 dilution), L26 (Dako; 1:200 dilution), and KP-1 (Dako; 1:500 dilution) as well as CD35 and OPD4.

At least one lymph node per case was stained with antisera to cytomegalovirus (Dako; 1:50 dilution) and herpes virus type 1 (1:100 dilution) to exclude concomitant viral infections. In all cases appropriate positive and negative controls were performed.

Histologic Classification of Lymphoid Tissues

In HIV-1–infected cases lymphoid architecture was classified as follicular hyperplasia without fragmentation (FH − FF), follicular hyperplasia with fragmentation (FH + FF), follicular involution (FI), and lymphoid depletion (LD) following the European Study Group on HIV Pathology consensus classification.[5,12] Thus, the morphologic appearance of the follicle is the focus of this classification system. Secondary follicles were defined as those containing actively transforming B cells within a follicular dendritic framework, highlighted by staining with anti-CD35. Primary follicles were composed of nontransformed small lymphocytes within a follicular dendritic network. Follicular hyperplasia without fragmentation is characterized by secondary follicles with prominent mantles and tingible body macrophages and by relatively intact mantle zones. Follicular hyperplasia with fragmentation denotes the presence of follicles that are greatly enlarged with irregular mantle zones and multifocal ingrowth of small lymphocytes that cause ill-defined borders of the germinal centers. In FI follicles are small, lack mantle zones and tingible body macrophages, and show inactive, sometimes scarred germinal centers. Because the precise distinction between FH + FF and FI depends partly on follicular size, at least one follicle was greater than 0.9 mm for inclusion in the former group for purposes of this study. If other areas of the follicle contained lytic follicles (ie, a mixture of pattern types) the lymph node was still classified as FH + FF. Many involuted follicles are difficult to discern without stains for the follicular dendritic cell network. Lymphoid depletion indicates a lack of follicles and diffuse infiltration of immunoblasts and plasma cells throughout the lymph node, with or without vascular proliferation. Paracortical plasmacytosis denoted aggregates of plasma cells filling more than half of one ×60 field. Intrafollicular plasma cells denoted the presence of any number of plasma cells in each follicle of a given lymph node. CD4 cell counts were estimated by quantitation of OPD4-positive cells in three 0.04 mm^2 areas with the use of an ocular grid. The three areas were chosen from the paracortex in patterns of follicular hyperplasia with or without fragmentation. In cases of FI or LD the paracortex was not readily identified, and three areas that qualitatively contained large numbers of OPD4-positive cells were chosen. The result was expressed as the mean of the three areas.

RESULTS

Patient Data

The mean age of the seropositive patients was 35.5 years, compared with 36.8 years for the seronegative patients. The cause of death was attributed to intravenous drug overdose in 45 of the 50 seropositive cases and to trauma in the remaining five. The cause of death in all the seronegative cases was drug overdose.

TABLE 2. Mean Number and Size of Follicles by Lymph Node Pattern

	Number ± SD	Size (mm) (range)
Seropositive cases		
FH-FF	17.7 ± 10.6	0.48 (0.25-0.9)
FH + FF	18.6 ± 13.1	1.38 (0.9-2.9)
FI	13.7 ± 12.0	0.44 (0.1-0.9)
LD	3.0 ± 1.1	0.18 (0.1-0.3)
Sinus histiocytosis	5.4 ± 3.3	0.11 (0.1-0.3)
Seronegative cases		
Paracortical hyperplasia	15.4 ± 6.5	0.30 (0.2-0.5)
Follicular hyperplasia	19.8 ± 14.1	0.44 (0.2-0.6)
Sinus histiocytosis	3.5 ± 3.2	0.18 (0.1-0.5)

Note: The mean size of the follicle represents the largest follicle in the section examined. Most follicles in the seropositive cases were secondary follicles. Among the seronegative cases, approximately half of the follicles in the follicular hyperplasia group were secondary. The remaining follicles in the seronegative cases were primary.

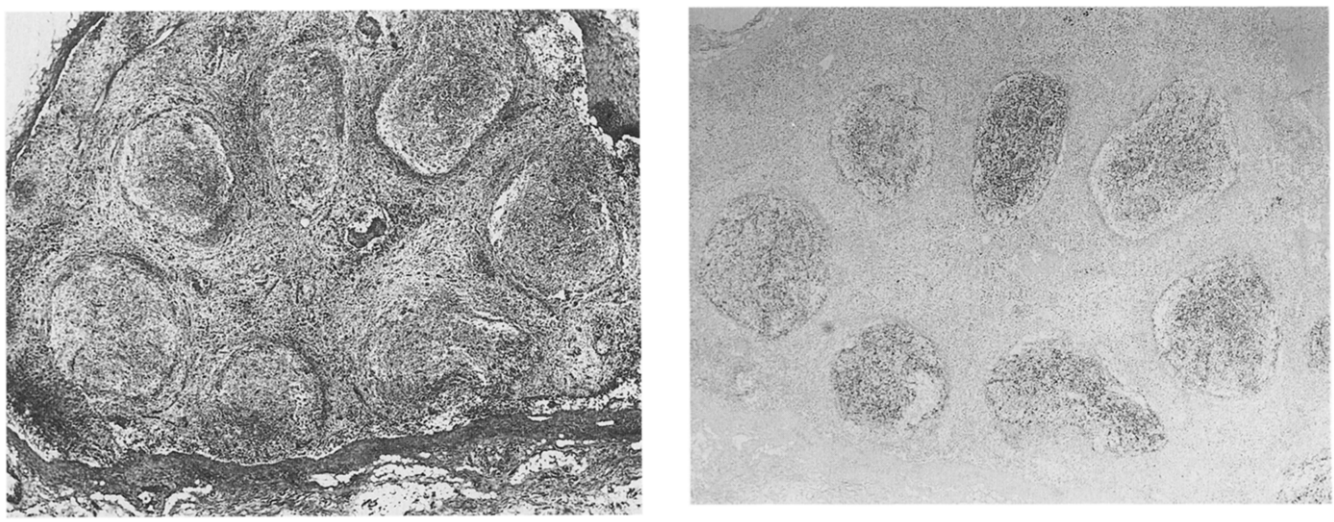

FIGURE 1. Follicular hyperplasia without fragmentation seen in an axillary lymph node from a 39-year-old man. Fifteen percent of lymph nodes from HIV-1–infected individuals contained unremarkable reactive secondary follicles. (Left: Hematoxylin-eosin stain. Right: Avidin-biotin anti-CD35, outlining follicular dendritic network. Magnification ×30.)

Lymph Node Histology: Seronegative Cases

Most of the lymph nodes in the seronegative cases demonstrated a predominant pattern of either sinus histiocytosis or paracortical hyperplasia (Table 1) with small primary follicles (Table 2). In 23% of lymph nodes approximately half of the follicles were secondary follicles; these were classified as follicular hyperplasia. Follicular hyperplasia was present in 42% of the inguinal nodes, 24% of the axillary nodes, 24% of the supraclavicular nodes, 20% of the mediastinal nodes, and 0% of the mesenteric nodes. Those cases that demonstrated follicular hyperplasia did not demonstrate loss of mantles zones, follicular fragmentation and fusion, or follicular involution. No lymph node in this group showed marked plasmacytosis, intrafollicular plasma cells, or giant cells. Dermatopathic lymphadenopathy was seen in 5% of lymph nodes, most of which were inguinal lymph nodes.

Lymph Node Histology: Seropositive Cases

Eighty-nine percent of lymph nodes had a reactive pattern containing secondary follicles (Figs 1 to 4): 15% demonstrated FH − FF, 37% demonstrated FH + FF, and 37% demonstrated FI. Lymphoid depletion was present in 9% of lymph nodes; two supraclavicular and three mesenteric lymph nodes demonstrated sinus histiocytosis. Primary follicles were rare. The distribution of the follicular pattern was similar among the lymph node group, although FH + FF was more prevalent in the inguinal (51%) and axillary (49%) lymph nodes compared with the mediastinal (31%), supraclavicular (28%), and mesenteric (24%) lymph nodes. The mean

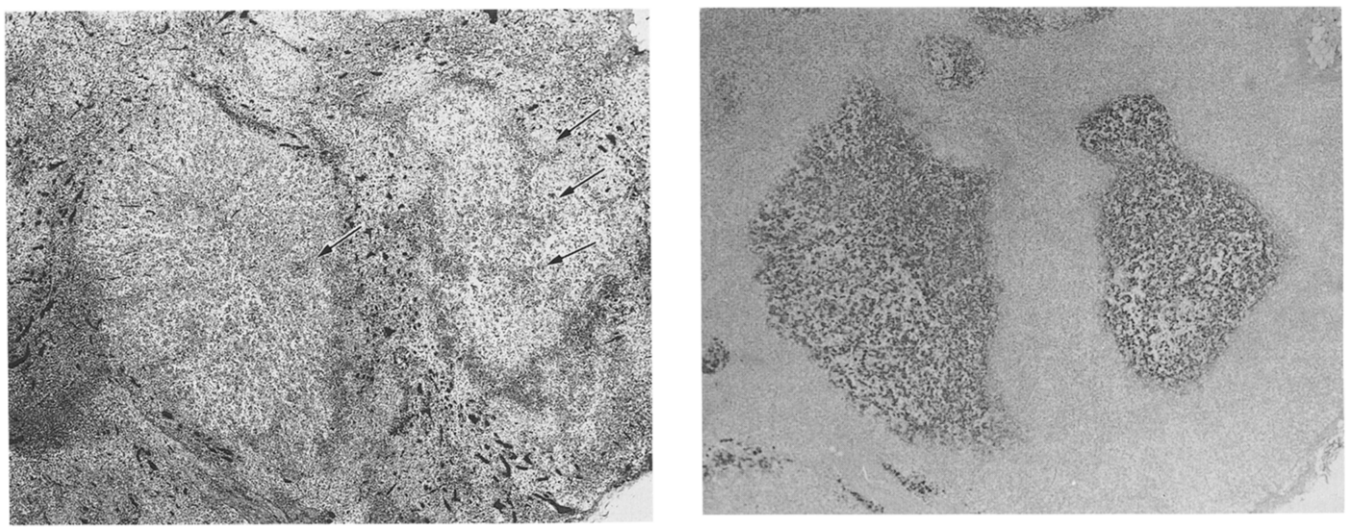

FIGURE 2. Follicular hyperplasia with fragmentation seen in a supraclavicular lymph node from a 47-year-old man. In contrast to Fig 1, the follicles shown here are much larger (note the same magnification), have multifocal invasion of germinal centers by small lymphocytes (arrows), and show obscuring of germinal center borders. (Left: Magnification ×30. Right: Avidin-biotin anti-CD35, outlining follicular dendritic network; magnification ×30.)

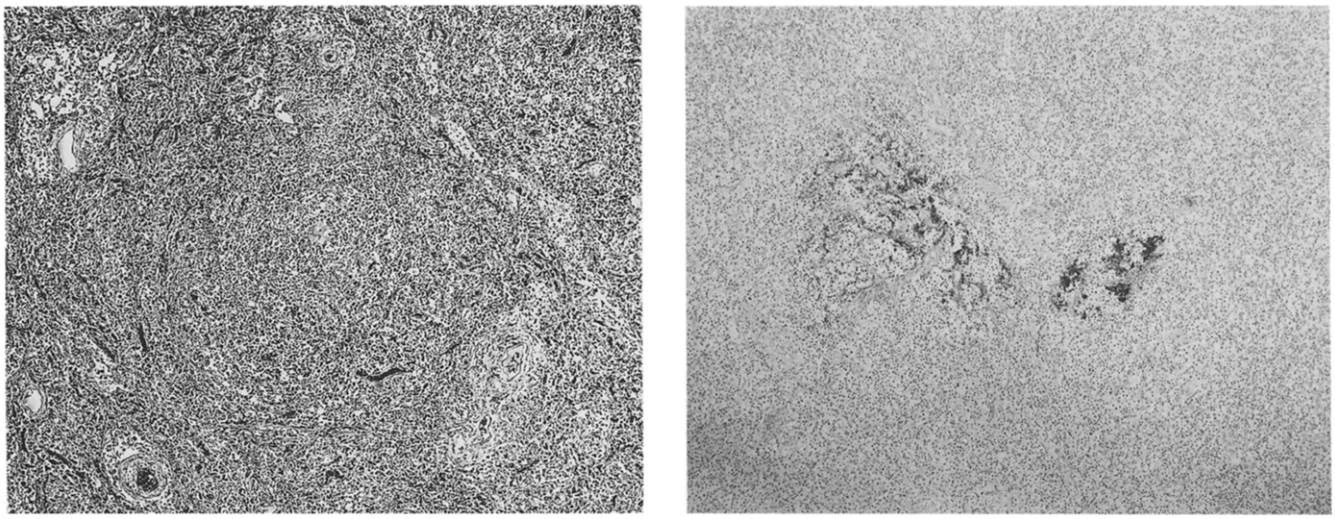

FIGURE 3. Follicular lysis seen in the axillary lymph node from a 40-year-old woman. In this example follicular remnants are not visible with the hematoxylin-eosin stain (left), unlike those follicles shown in Figs 1 and 2. (Right) A photomicrograph from the same area stained for the reticular dendritic cell network demonstrates a small, lysed follicle. (Avidin-biotin anti-CD35; magnification ×75.)

numbers of follicles per lymph node section are presented in Table 2. The total number was similar to that of the seronegative cases. However, most follicles in the infected nodes were secondary follicles, whereas primary follicles predominated in control nodes. The mean size of secondary follicles per lymph node was nearly threefold greater in FH + FF than in any other lymph node pattern in either seropositive or seronegative cases (Table 2).

Intrafollicular and paracortical plasma cells were present in more than half of the lymph nodes and increased with progressive follicular abnormality (Table 3). The increased prevalence compared with lymph nodes from seronegative controls was highly significant ($P < .001$).

Warthin-Finkeldey–type giant cells were seen in 29 of 50 autopsies. In 26 of these cases they were present in more than one lymph node, and in four of these cases they were present in all five lymph nodes examined. Warthin-Finkeldey–type giant cells were most prevalent in cases with FH + FF (Table 1; Figs 5 and 6).

For a given individual there was good concordance of histologic pattern among lymph nodes from diverse anatomic sites. In 14 autopsies the lymph nodes and lymphoid tissues showed FH − FF or FH + FF; the mean age of these individuals was 34.6 years. In 30 autopsies FH + FF or FI was present; the mean age of these individuals was 37.7 years. In the remaining six autopsies FI or LD was seen; the mean age of these individuals was 41.3 years. In all cases histologic changes were limited to two patterns. In 17 cases all nodes were the same type (one FH − FF, six FH + FF, eight FF − FF, and two LD); in 10 cases all but one node were the same type (three LD/FI, two FH − FF/FH + FF, two FI/LD, one FH + FF/FI, one FI/FF + FF, and one FF + FF/FF − FF). In the remaining 23 cases there was a 2:3 ratio between two histologic patterns (15 FI/FH + FF, six FH − FF/FH + FF, and two FI/LD). Dermatopathic lymphadenopathy was present in 7% of lymph nodes, primarily inguinal nodes.

Lymph Node Size

The lymph nodes from seropositive cases were larger than those from seronegative cases ($P < .001$, Student's *t*-test). The lymph nodes from seropositive cases of each histologic pattern, with the exception of lymphoid depletion and sinus histiocytosis, also were larger than those of the seronegative cases ($P < .01$). Of all the lymph nodes from seropositive cases, 90.2% were smaller than 2.0 cm. The mean sizes of the lymph nodes from the seropositive cases were 16.7 mm for the axillary nodes, 16.1 mm for the inguinal nodes, 15.0 mm for the mediastinal nodes, 14.9 mm for the mesenteric nodes, and 11.1 mm for the supraclavicular nodes. The mean sizes of the lymph nodes from the seronegative cases were 12.1 mm for the axillary nodes, 12.2 mm for the inguinal nodes, 13.8 mm for the mediastinal nodes, 7.6 mm for the mesenteric nodes, and 6.2 mm for the supraclavicular nodes.

Immunohistochemistry

In the lymph nodes from the seropositive cases the number of CD4-positive cells decreased as the lymphoid pattern progressed (Table 4). The differences from one step to the next were significant at each step ($P < .01$, Student's *t*-test) and the number of CD4 cells in the seropositive nodes with FI or LD was less than that of the seronegative nodes ($P < .001$). The paucity of CD4 cells in FI appeared to be due to a decrease in interfollicular areas.

Staining with labeled anti-CD35 demonstrated the follicular dendritic cell network and follicular outlines, facilitating the classification of FH − FF, FH + FF, and FI (Figs 1 to 4). Staining with anti-p24 antigen demonstrated antigen in a follicular dendritic cell distribution

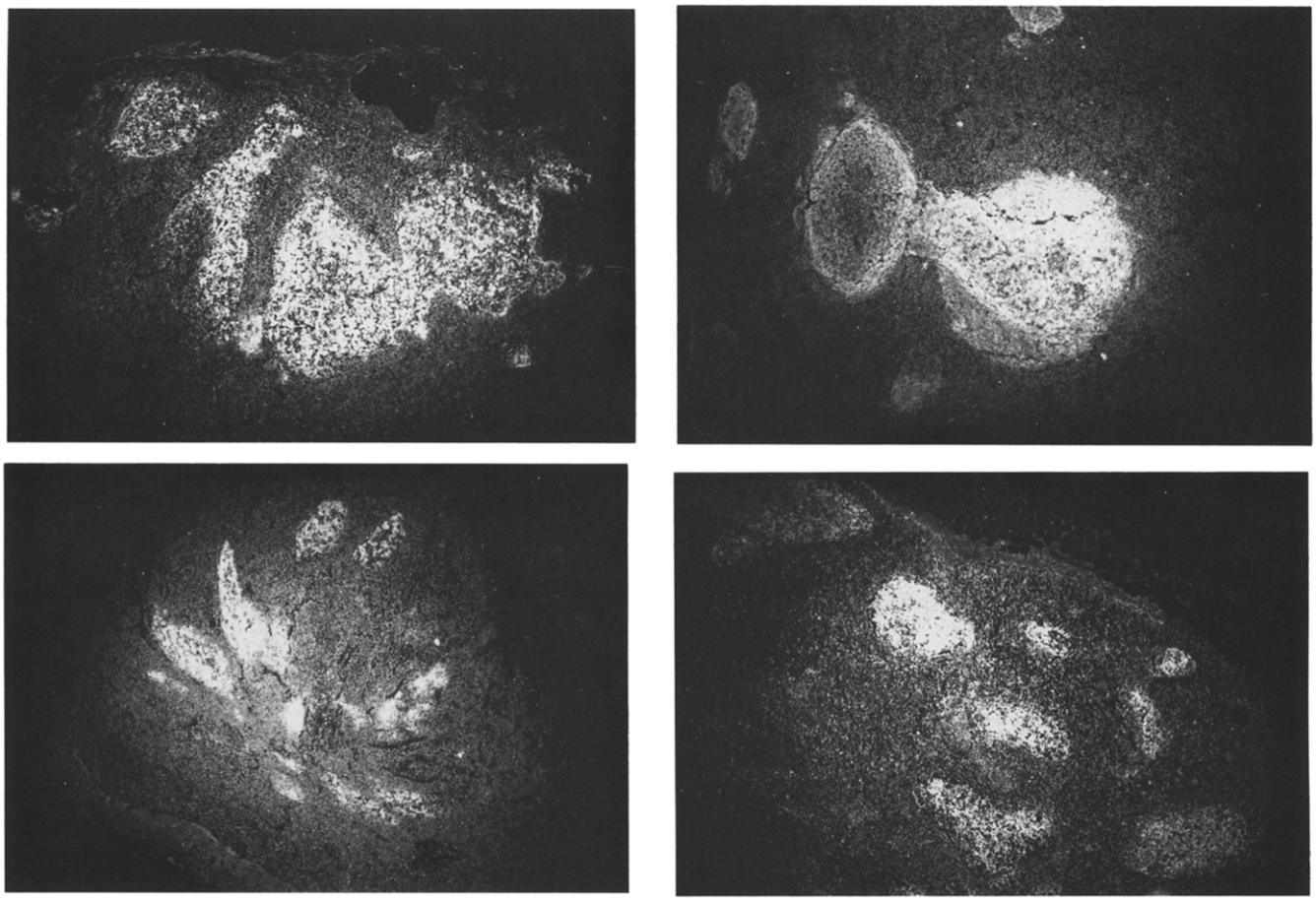

FIGURE 4. Comparison of FH + FF and FI. These two histologic patterns are similar in that there is loss of mantles, ingrowth of small lymphocytes, and irregular follicles. The major distinction is in the size of the follicles. In the top left and right panels, which depict FH + FF, there are greatly enlarged follicles attaining a size of at least 0.9 mm. In the bottom left and right panels there are smaller involuted follicles that are no larger than 0.9 mm. All photomicrographs were acquired under darkfield microscopy to highlight diaminobenzidine. (Immunohistochemical preparation using anti-CD35 for follicular dendritic cells; magnifications ×30.)

in a minority of lymph nodes from the seropositive cases. Lymph nodes showing FH − FF were most often positive (43%), followed by FH + FF (29%) and FI (19%). Staining was not observed in other lymphoid patterns or nodes from the seronegative individuals.

Cytomegalovirus and herpes virus 1 antigen were not detected in any lymph node. Warthin-Finkeldey–type giant cells were negative for endothelial markers (Qbend, factor VIII-related antigen), histiocytic marker (Kp-1), T-cell marker (CD3), B-cell marker (L26), follicular dendritic cell marker (CD35), and interdigitating reticulum cell marker (S-100).

TABLE 3. Presence of Plasma Cells by Lymph Node Pattern

	No. of Lymph Nodes With Plasma Cells (%)	
	Intrafollicular*	Paracortical†
Seropositive cases		
FH-FF	14/34 (41)	9/34 (26)
FH + FF	60/87 (69)	35/87 (40)
FI	79/87 (91)	61/87 (70)
LD	NA	14/20 (70)
Seronegative cases		
Any pattern	0/13	0/48 (0)

Abbreviation: NA, not applicable.
* Presence of at least one plasma cell in each follicle.
† Presence of aggregates of plasma cells in paracortical areas.

Histology, Other Lymphoid Tissues: Seropositive Cases

Of the 28 tonsils, seven showed FH − FF, five showed FH + FF, 10 showed FI, and six showed LD. Warthin-Finkeldey–type giant cells were present in 12 cases and were distributed among all histologic patterns. In 11 of 18 cases with Peyer's patches WF-type giant cells were present; WF-type giant cells were seen in only two of 35 splenic tissues. Twenty-five spleens demonstrated secondary follicles in the white pulp; in the remaining spleens the white pulp consisted of small lymphocytes and plasma cells.

DISCUSSION

Histology

This study demonstrates that lymphadenopathic changes characteristic of asymptomatic HIV-1 infection

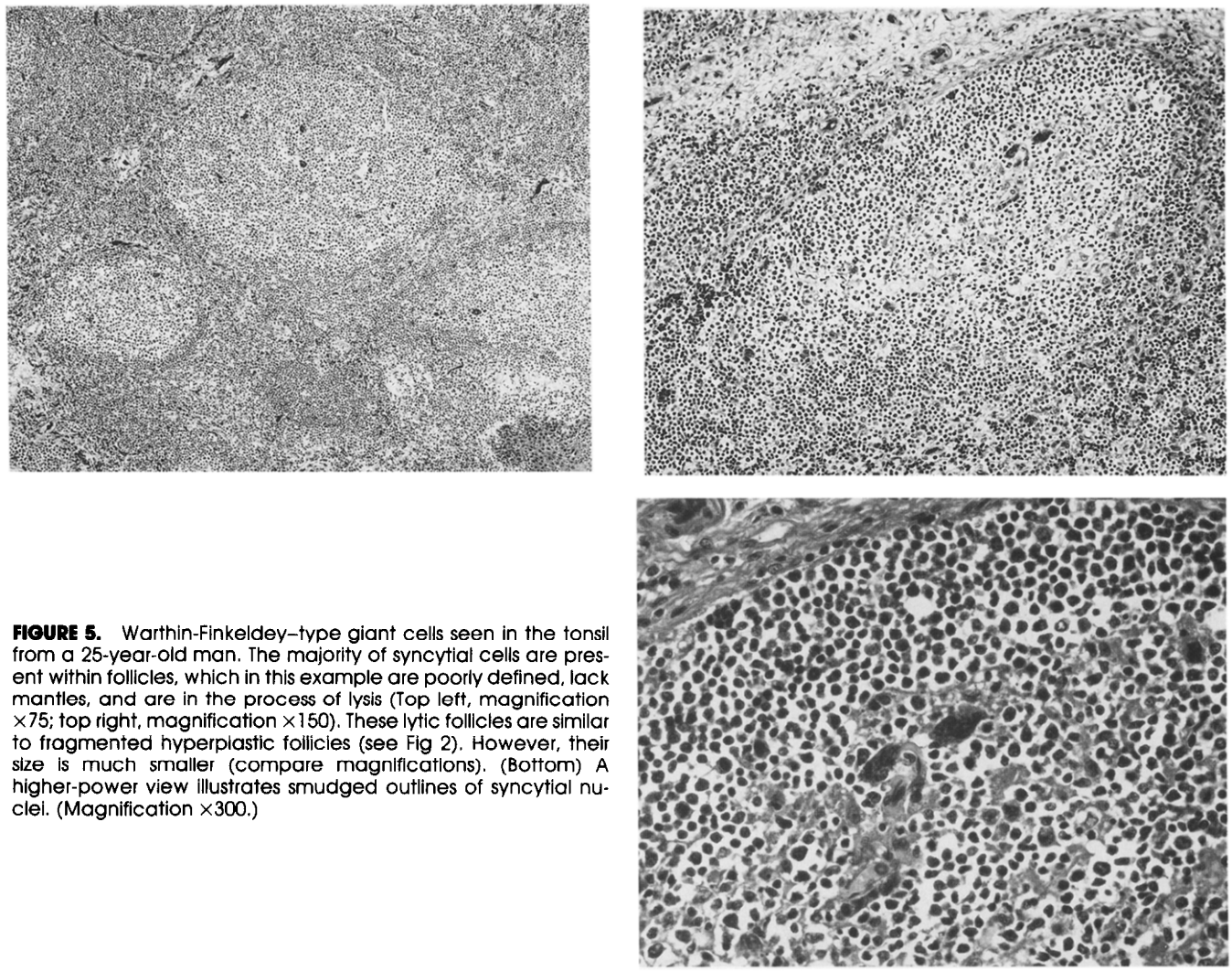

FIGURE 5. Warthin-Finkeldey–type giant cells seen in the tonsil from a 25-year-old man. The majority of syncytial cells are present within follicles, which in this example are poorly defined, lack mantles, and are in the process of lysis (Top left, magnification ×75; top right, magnification ×150). These lytic follicles are similar to fragmented hyperplastic follicles (see Fig 2). However, their size is much smaller (compare magnifications). (Bottom) A higher-power view illustrates smudged outlines of syncytial nuclei. (Magnification ×300.)

occur diffusely throughout the lymphoid system, involve lymph nodes that are not grossly enlarged, and are relatively uniform in various lymph node groups from a given individual. Previous studies of the lymphoid pathology of HIV-1 disease have been based only on patients with lymphadenopathy and have not compared the features of one lymph node to another in an individual.

These results suggest that random biopsy of a single, non-enlarged lymph node in an asymptomatic HIV-1–infected individual may reflect the lymphoid pathology elsewhere in the body. Follicular alterations were absent in only 2% of studied nodes, and these represented mesenteric and supraclavicular lymph nodes. The HIV-1–associated follicular alterations appear in all lymph node groups in about equal proportions, with two exceptions. Axillary and inguinal nodes were more likely to demonstrate a pattern of FH + FF than other lymph nodes. This may be a result of portal of entry of virus, chronic stimulation by intravenous drugs, or other unknown factors.

Because most of our seropositive cases were drug abusers, a comparison to control lymph nodes was necessary to determine whether there are stimulative effects of intravenous drug abuse on the lymphoid system. The percentage of lymph nodes demonstrating secondary follicles was significantly increased in the seropositive cases, although the total number of follicles was similar to that of the control nodes. In addition, the size of follicles was markedly increased in HIV-1–seropositive individuals in the stages of FH + FF and, to a lesser extent, FH − FF. This difference implies that there is chronic stimulation of follicles in the HIV-1–seropositive individuals and that this stimulation is not a consequence of chronic stimulation from injection of foreign substances. In addition to follicular size, the generalized follicular stimulation in HIV-1–infected individuals resulted in larger lymph nodes than in those seen in the seronegative controls. This difference was statistically significant and greatest in HIV-1–infected lymph nodes showing FH + FF. However, the difference represented a less than 50% increase in size and was not great enough to cause palpable lymphadenopathy.

These data suggest that there is a long phase of mild generalized lymphadenopathy in HIV-1–infected individuals that involves all lymph nodes. Although an acute phase of greatly enlarged lymph nodes is recognized in a subset of HIV-1 patients and has been termed "AIDS-related complex," it appears likely from our data that a mild lymphadenopathy of extended dura-

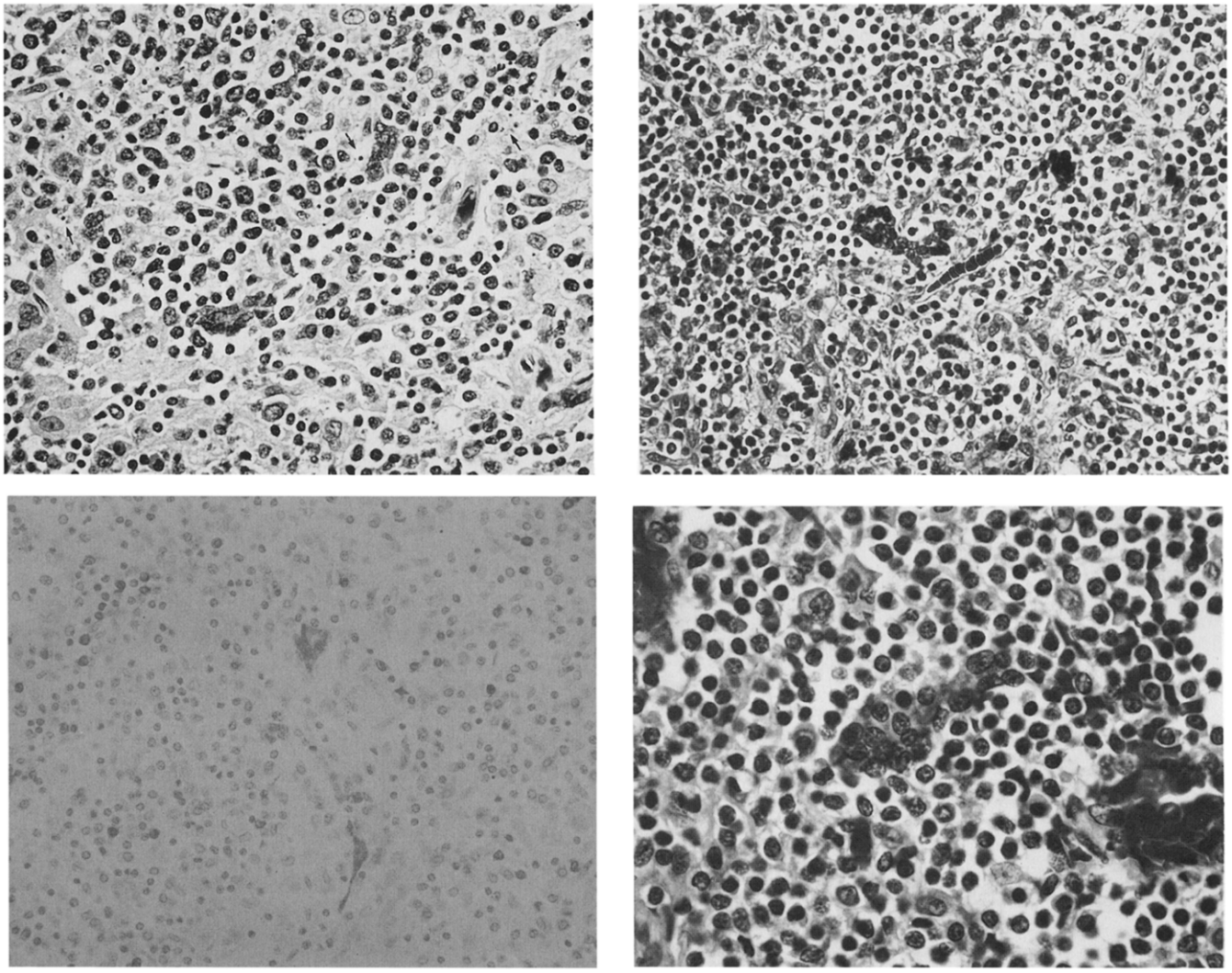

FIGURE 6. Warthin-Finkeldey–type giant cells within germinal center (Top left) (note the tingible bodies [arrows]) and (top right) interfollicular area. (Magnifications ×300.) (Bottom left) A higher-power view suggests that the cells are of lymphoid origin, although marker studies were inconclusive. (Magnification ×500.) (Bottom right) There are scattered CD4 cells in a lymph node with lymphoid depletion and absent germinal centers; WF-type giant cells do not appear to express this marker. (Anti-OPD4; magnification ×300.)

tion is the rule in HIV-1 disease and that it is slightly more pronounced in lymph nodes with FH − FF or FH + FF.

Because clinical staging was not possible in our cases, we cannot state that there is a temporal progression between the stages of FH − FF, FH + FF, FI, and LD. However, other investigators have presented data to support this concept[10] and we demonstrated decreasing CD4 counts and increasing age in individuals with advanced stages of follicular degeneration and an increase in plasmacytosis. Therefore, we can speculate that these stages indeed reflect temporal progression of HIV-1 disease. Because the lymph nodes of most infected individuals in this study demonstrated FH + FF and FI, we presume that these patterns occur during a long period of clinically latent HIV-1 disease. The stages of FH − FF and LD probably occur as relatively short periods at the beginning and end, respectively, of asymptomatic HIV-1 disease. Further study of non-enlarged lymph nodes from clinically staged asymptomatic individuals is necessary to determine whether histopathologic staging is relevant in asymptomatic HIV-1 disease.

Our study demonstrates that WF-type giant cells are present in all histopathologic stages, are present both within and outside of follicles, and are seen in lymph nodes of half of the patients with asymptomatic HIV-1 infection. In previous reports WF-type giant cells have been described only in lymph nodes showing FH − FF; our data suggest that they are not restricted to this pattern, but may be found in FH + FF, FI, and LD.[12] We have shown an especially high percentage of Peyer's patches with WF-type giant cells (61%). Because the formation of syncytia in vitro is dependent on viral strain,[14] the high incidence of WF-type giant cells may reflect a similar genetic strain of HIV-1 in our patient population. Most of the individuals in our study were taken from a single urban center and acquired infection by intravenous transmission; therefore, many may have been infected with a similar strain of virus.

We were unable to determine the cell type of the WF-type giant cells, despite an attempt at immunophe-

TABLE 4. Semiquantitative CD4 Cells by Lymph Node Pattern

	Mean CD4 Count/ 0.04 mm² ± SD (n)
Seropositive cases	
FH-FF	122 ± 36.3 (15)
FH-FF	96 ± 34.7 (60)
FI	60 ± 34.3 (60)
LD	25 ± 15.8 (13)
Seronegative cases	
Paracortical hyperplasia	147 ± 65.8 (6)
Follicular hyperplasia	147 ± 37.6 (7)
Sinus histiocytosis	127 ± 29.5 (15)

Abbreviations: FH-FF: follicular hyperplasia without fragmentation; FH+FF: follicular hyperplasia with fragmentation; FI: follicular involution; LD: lymphoid depletion.

notyping using a number of antibodies. An alteration or loss of cell receptors in WF-type giant cells may explain their lack of immunoreactivity. Multiple cell types may be involved in syncytia formation. In cases of measles these cells have been shown to express both T-cell[15,16] and B-cell[16] markers.

Our conclusions regarding the prevalence of WF-type giant cells, uniformity of histologic changes, and prevalence of different histologic patterns in early HIV-1 disease have been demonstrated only for individuals infected by route of intravenous drugs. It is not known whether the method of viral transmission affects histologic changes. However, it is reasonable to assume that these histologic changes may be similar in sexually acquired infection.

Pathogenesis of Human Immunodeficiency Virus Lymphadenopathy

Although it is likely that progressive stages of FH – FF, FH + FH, FI, and LD mirror clinical deterioration of the immune status, the mechanism of this deterioration and the reasons for the long latency period of HIV-1 disease are not entirely understood. In situ hybridization studies for HIV-1 RNA have demonstrated that the majority of viral RNA reside in the follicular dendritic cell network.[17,18] Stimulation of HIV-1–specific CD4 cells may result in their active infection on circulation through the germinal center. Progressive lysis of infected T cells will result in T-cell depletion in the progressive lymph node stages that we have demonstrated in this study. These results are supported by previous findings of decreased numbers of CD4 cells in lymph nodes from patients with AIDS and HIV-related lymphadenopathies.[19-21]

However, a direct HIV-1–mediated cytopathic effect on T lymphocytes residing in lymph nodes has not been substantiated. A significant population of T cells latently infected with HIV-1 and a correlation between viral burden and histopathologic changes have yet to be documented. Other theories explaining the in vivo destruction of T cells in HIV-1–infected patients include HIV-1–induced autoimmunity against T lymphocytes[22] and coinfections with other viruses, including Epstein-Barr virus, herpes viruses, cytomegalovirus, and others.[11]

The pathogenesis of follicular fragmentation and involution has been attributed to a direct cytopathic effect of HIV-1 in follicular dendritic cells.[23] Despite ultrastructural evidence of HIV-1 replication within follicular dendritic cells,[24] it currently is believed that these cells are not directly infected but contain HIV-1 as antigen-antibody complexes on their cell processes.[5] The lysis of follicular dendritic cells may be a result of an influx of cytotoxic T cells that is observed in follicular fragmentation[25] and a concomitant lack of T-helper cells that are required for the integrity of the follicular dendritic cell network.[26]

Intrafollicular and paracortical plasmacytosis is a prominent finding in lymph nodes infected with HIV-1, and increases as follicular destruction progresses, as we have shown in this study. The phenomenon of mature antibody-producing B-cells developing within germinal centers is consistent with the persistence of antigen-antibody complexes in the presence of free antigen.[27] The persistence of antigen-antibody complexes on cell processes reflects incomplete neutralization of HIV-1 by antibody and ongoing infection of newly recruited T cells. Intrafollicular plasma cells also are present in autoimmune diseases, which are characterized similarly by immune complex deposition.[11] In HIV-1 disease there is general stimulation of B-cell immunity, which has been demonstrated both in vivo[28] and in vitro.[29] Stimulation of the antibody-producing cells may be partly an indirect effect of the destruction of T-cell immunity.

Conclusions

Asymptomatic infection with HIV-1 in intravenous drug addicts is characterized by a generalized mild lymphadenopathy. The most striking lymphadenopathic changes are the irregular enlargement and eventual involution and destruction of lymphoid follicles in a relatively simultaneous manner throughout the body. Follicular fragmentation and involution are the most common lymph node patterns. Warthin-Finkeldey–type giant cells are common and are most numerous in those nodes showing follicular hyperplasia with fragmentation. As there is progressive lysis of germinal centers, there is an increase in the number of intrafollicular and extrafollicular plasma cells and a decrease in intrafollicular and extrafollicular CD4-positive cells.

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