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[Original Article]

Lymphoid Changes of the Nasopharyngeal and Palatine Tonsils that are Indicative of Human Immunodeficier Infection: A Clinicopathologic Study of 12 Cases

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Abstract

We report 12 cases in which the histomorphologic changes of the nasopharyngeal tonsils (adenoids) or palatine tonsils suggest infection with the human immunodeficiency virus (HIV). The patients included 10 men and two women, aged 20 to 42 years (median, 33 years). The clinical presentation included airway obstruction, pharyngitis, fever, and a tonsillar or adenoidal mass lesion. Histologic evaluation of the excised adenoids or tonsils in 10 of the cases demonstrated a spectrum of changes including florid follicular hyperplasia, follicle lysis, attenuated mantle zone, and the presence of multinucleated giant cells (MGC). The latter characteristically localized adjacent to the surface or tonsillar crypt epithelium. Two of the 12 cases showed marked lymphoid depletion with absent germinal centers, plasmacytosis, and stromal vascular proliferation. Immunohistochemical evaluation for HIV p24 core protein showed reactivity in 10 of 12 cases localized to follicular dendritic cell network (FDC), the MGC, scattered interfollicular lymphoid cells, and cells identified within the surface or crypt epithelium. Localization of viral RNA by in situ hybridization paralleled the HIV p24 immunohistochemical findings. Additional significant findings included the presence of both CD-68 and S-100 protein in the MGC and the presence of S-100 protein in dendritic cells. Other than HIV, no microorganisms were identified. At the time of presentation, eight patients were not known to be a risk for HIV infection, nor were they known to be HIV infected or suffering from AIDS. In these patients, HIV infection was suspected on the basis of the histologic changes seen in the resected tonsillar and adenoidal tissue. Serologic evaluation (by enzyme-linked immunosorbent assay), confirmed the presence of HIV infection. Our findings suggest the possibility of HIV dissemination through the upper aerodigestive tract mucosa via target cells, such as intraepithelial dendritic cells, submucosal macrophages, and T-lymphocytes. Subsequent presentation of viral antigens to the tonsillar and adenoidal lymphoid tissues results in enlargement of these structures that clinically may simulate a neoplastic proliferation but causes histomorphologic changes that are highly suspicious for HIV infection even in asymptomatic HIV-positive patients.

Infection with the human immunodeficiency virus (HIV) leads to a chain of events within the host immune system that ultimately results in immunosuppression with the development of acquired immunodeficiency syndrome (AIDS). Death generally ensues secondary to infection by opportunistic organisms (73,74). Although there are several hypotheses about how HIV causes cell death, the precise cytopathic mechanism is not completely understood (24,51); however, the critical pathogenic event in HIV infection is both a quantitative decrease and the functional compromise of CD4+ T-cell lymphocytes (17,39). Irrespective of the mechanism, the chain of events from the time of HIV infection to the development of immune suppression appears to follow a similar course. Lymphocytes and the cells of the monocyte/macrophage system represent a major target of HIV

(15,29,34). These cells serve as a reservoir for viral persistence and transmission (15,65). Following infection, these cells are believed to transport the virus to lymph nodes, where the lymphoid germinal centers have been shown to be reservoirs of HIV RNA (21). Also included within the complex microenvironment of the body's immune system are the dendritic cells, which are identified throughout the body, including in the peripheral blood, in lymphoid organs within germinal centers and T-dependent interfollicular regions, and in nonlymphoid organs such as skin and mucous membranes (59,68). Dendritic cells represent potent antigen-processing cells and activators of T cells (68). In addition to the blood mononuclear cells, dendritic cells play a major function in the transmission of HIV to cells (14) and represent a major reservoir for HIV, facilitating infection of CD4-positive T-helper cells (66).

Presentation of HIV to lymphoid tissues via blood mononuclear cells and dendritic cells results in changes at the molecular level that result in enlargement of the infected lymphoid tissues in the early and latent stages of disease (4,16,31,75) as well as causing enlargement of infected extranodal lymphoid tissues, such as the tonsils and adenoids (1,62,69,75). HIV infection results in a spectrum of morphologic changes that may represent the initial manifestation of HIV infection in otherwise asymptomatic patients. Similar to the direct transmucosal infection of HIV transmission that has been recently proposed in other mucosal sites (45), our findings support the possibility of transmission of HIV via the mucosa of the upper aerodigestive tract.

MATERIALS AND METHODS

A search of the files of Otolaryngic Pathology Tumor Registry at the Armed Forces Institute of Pathology identified 12 cases of nasopharyngeal and tonsillar specimens showing histologic changes compatible with HIV infection as described in lymph nodes (4,16,31,75). Hematoxylin and eosin (H&E)-stained slides and paraffin-embedded blocks were available in all cases. Sections from each case were stained with Gram (Brown and Hopps), mucicarmine, periodic acid-Schiff, Warthin-Starry, Gomori methenamine silver, and acid-fast bacilli to look for the presence of a microorganism. Follow-up information was available in all cases.

Immunohistochemical studies were performed in all cases. Five-micron sections from paraffinembedded tissue blocks were prepared for immunohistochemical analysis according to the standardized avidin-biotin complex method of Hsu (30). The basic commercially prepared antibody panel for each case included CD45RB (mouse monoclonal, 1:400 Dako, Carpinteria, CA, U.S.A.), CD20 (L-26) (mouse monoclonal; 1:200; Dako), CD45RO (UCHL-1) (mouse monoclonal; 1:200; Dako), CD3 (rabbit polyclonal; 1:500; Dako), OPD4 (mouse monoclonal; 1:100; Dako), cytokeratin cocktail (AE1/AE3 and CK1) (mouse monoclonal, 1:400; AE1/AE3, Dako; CK1, Boehringer Mannheim, Indianapolis, IN, U.S.A.), S-100 protein (rabbit polyclonal, 1:800; Dako), CD21 (mouse monoclonal; 1:150; Dako), CD68 (KP1) (mouse monoclonal; 1:100; Dako), HIV p24 (mouse monoclonal; 1:100; Dako), Epstein-Barr virus latent membrane protein (mouse monoclonal; 1:50; Dako), herpes simplex virus (rabbit polyclonal; 1:200; Dako), and cytomegalovirus (mouse monoclonal; 1:800; Chemicon, Temecula, CA, U.S.A.). Of the above antibodies, cytokeratin required predigestion for 3 min with 0.05% Protease VIII (Sigma Chemical Co., St. Louis, MO, U.S.A.) in 0.1*M* phosphate buffer at a pH of 7.6 at 37°C. Sections were counterstained with Mayer's hematoxylin. Positive and negative controls were used throughout.

The protocol of Fox et al. was followed with minor modification for the detection of viral RNA (21). This method uses transcription riboprobes radiolabeled with ^{35}S (6,21). Positive controls included lymph nodes with known viral RNA and cell suspensions, as previously described (6), negative control probes were used as previously published (5) and consisted of sense probes. Each slide was run parallel using sense and antisense probes.

RESULTS

Clinical

The clinical details are listed in Table 1. In brief, there were 10 men and two women ranging in age from 20 to 42 years. The median age was 33 years. The clinical presentations varied and included nasal congestion, airway obstruction, sore throat (pharyngitis), otitis media unresponsive to antibiotic therapy, otalgia, facial weakness, fever, and a nasopharyngeal or tonsillar mass. Clinical evaluation demonstrated the presence of enlarged tonsils or adenoids. In addition, two of the patients (cases 2 and 5) had unilateral cervical adenopathy. Of the entire group of 12 patients, four were known or suspected at the time of presentation to be infected with HIV or suffering from AIDS; all of these patients were seropositive for HIV but without evidence of opportunistic infections. The remaining eight patients were not known to be HIV infected and were not known to be in any of the risk groups associated with possible HIV infection. Other than enlarged tonsils or adenoids, these patients presented without

associated with possible HIV infection. Other than enlarged tonsils or adenoids, these patients presented without any of the clinical stigmata of HIV infection. The enlargement of the tonsils or adenoids clinically raised the concern for a neoplasm, prompting surgical removal of the enlarged organ. On the basis of histologic features suggestive of possible HIV infection (see below), serologic analysis by enzyme-linked immunosorbent assay (ELISA) was performed in seven of these eight patients. All seven patients were HIV positive. One patient (case 3) refused to be tested, but immunohistochemical and in situ hybridization performed on her tissue specimens showed the presence of HIV. When known, the risk factors for HIV infection included homosexuality, blood transfusions, or intravenous drug abuse. In some of the patients who were not known to be HIV infected and did not admit to any of the above risk factors, it is possible that HIV infection was acquired through heterosexual transmission. We do not, however, have this information definitively. Follow-up was limited, as many of the patients did not remain under a physician's care. CD4 T-lymphocyte counts were available in three of the patients. In case 2, the CD4 count was 120 at the time his adenoids were removed; in case 9, the CD4 count at 2 years after surgery was 202; in case 11, the CD4 count was 247 at 1 year after surgery. Of the six patients with adequate follow-up, two died of disease, three developed AIDS and were in the terminal stages of disease, and one was alive without progression of disease 4 years after diagnosis.

Case/ age (yr)/ gender	Symptoms	HIV/AIDS status at presentation	Pathology	IHC (HIV p24)	ISH	Serologic (ELISA) HIV status; follow-up
1/20/M	Unilateral conductive hearing loss; NP mass	Not known or suspected	FFH, FI, Giant cells	FDC; giant cells; scattered lymphocytes; intraepithelial cells	Similar to HIV p24 immunoreactivity	HIV + ; lost to follow-up
2/42/M	NP mass and unilateral cervical adenopathy	Not known or suspected	Diffuse changes	Negative	Not done[a]	HIV + ; dead of disease
3/36/F	Airway obstruction × 6 mo; 3–4 cm NP mass	Not known or suspected	FFH, FI, Giant cells	FDC; giant cells; scattered lymphocytes; intraepithelial cells	Similar to HIV p24 immunoreactivity	Refused testing; lost to follow-up
4/35/M	Pharyngitis (tonsillitis) × several mo unresponsive to antibiotics; esophageal candidiasis	Known AIDS patient	Diffuse changes	Negative	Negative	HIV + ; dead of disease
5/20/M	Hypertrophic adenoids and unilateral cervical adenopathy	Not known or suspected	FFH, FI, Giant cells	FDC	FDC; scattered lymphocytes	HIV + ; no evidence of ARC/AIDs 4 yr after diagnosis
6/24/F	3 cm NP mass; history of open heart surgery for mitral valve replacement	HIV infection suspected	FFH, FI, Giant cells	FDC; giant cells; scattered lymphocytes; intraepithelial cells	FDC; scattered lymphocytes intraepithelial cells	HIV + ; lost to follow-up
7/37/M	Cocaine abuser had surgery to correct deviated septum at which time a NP mass was seen	Not known or suspected	FFH, FI, Giant cells	FDC; giant cells; scattered lymphocytes; intraepithelial cells	Similar to HIV p24 immunoreactivity	HIV + ; developed AIDs presently on supportive therapy
8/29/M	Sudden onset of R facial weakness and hypertrophic adenoids	Known HIV + × 5 yr	FI; Giant cells	FDC; giant cells; scattered lymphocytes; intraepithelial cells	Similar to HIV p24 immunoreactivity	HIV + ; Lost to follow-up
9/37/M	Nasal discharge and fevers; hypertrophic adenoids	Known HIV +	FI; giant cells, plasmacytosis	FDC; giant cells; scattered lymphocytes; intraepithelial cells	Similar to HIV p24 immunoreactivity	HIV + ; developed AIDS presently on supportive therapy
10/42/M	Bilateral otitis media unresponsive to antibiotics; enlarged adenoids with obstruction of posterior choanae	Not known or suspected	FI; giant cells	FDC; giant cells; scattered lymphocytes; intraepithelial cells	Similar to HIV p24 immunoreactivity	HIV + ; lost to follow-up
11/32/M	1 yr history of difficulty breathing and postnasal drip; NP mass	Not known or suspected	FFH, FI, giant cells	FDC; giant cells; scattered lymphocytes; intraepithelial cells	Similar to HIV p24 immunoreactivity	HIV + ; pulmonary manifestations 1 yr after diagnosis
12/24/M	Airway obstruction; 3-cm polypoid NP mass extending to base of skull as seen on CT scan	Not known or suspected	FFH, FI, giant cells	FDC; giant cells; scattered lymphocytes; intraepithelial cells	Similar to HIV p24 immunoreactivity	HIV + ; lost to follow-up

HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; IHC, immunohistochemistry; ISH, in situ hybridization; ELISA, enzyme-linked immunosorbent assay; NP, nasopharynx; FFH, florid follicular hyperplasia; FI, follicular involution; FDC, follicular dendritic cells; CT, computed tomography.
[a] Material unavailable for study.

TABLE 1. *Clinicopathologic features: HIV tonsils and adenoids*

Histology

The histomorphologic changes in 10 patients included the presence of florid follicular hyperplasia with and without follicular fragmentation. These findings included the presence of markedly expanded, irregularly shaped,

or convoluted-appearing germinal centers (Fig. 1). The cells within the enlarged germinal centers included mature lymphocytes, activated lymphocytes, numerous tingible body macrophages, and the presence of mitotic figures. The mantle zone lymphocytes surrounding the hyperplastic follicles were attenuated or partially lost (Fig. 1). Foci in which small lymphocytes "invaded" the germinal centers resulted in fragmentation of the germinal centers, creating a "motheaten" appearance with ill-defined borders (Fig. 2). These changes are referred to as follicle lysis. In these same cases, there were areas of follicular involution characterized by small follicles with disappearance of the tingible body macrophages. The involuted follicles had no clearly defined mantle zones (Fig. 2). Additional findings included the presence of monocytoid B-cell hyperplasia, paracortical and interfollicular zone expansion with immunoblasts and plasma cells, interfollicular clusters of high endothelial venules, intrafollicular hemorrhage, and the presence of multinucleated giant cells (MGC). The MGC were characterized by the presence of numerous nuclei usually arranged along the periphery of the cytoplasm but occasionally clustered within the central portion of the cytoplasm (Fig. 3). The MGC were randomly distributed throughout the lymphoid tissue and were occasionally seen within germinal centers; however, the giant cells characteristically clustered adjacent to the surface epithelium or the tonsillar crypt epithelium and, in particular, to squamous rather than respiratory epithelium (Fig. 3).

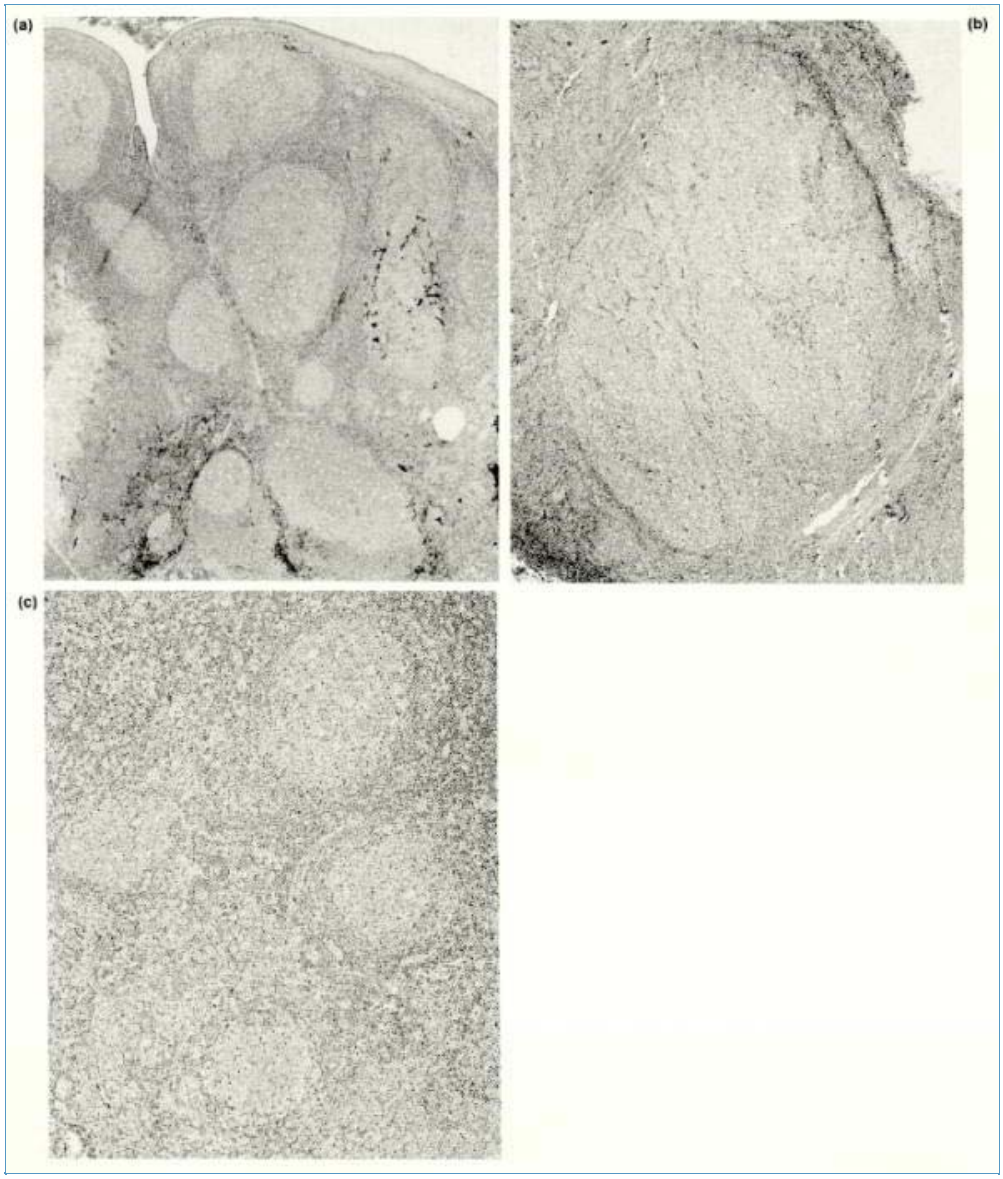
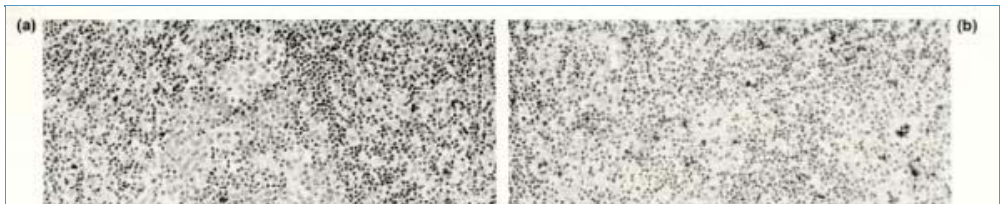


FIG. 1 a–c. Early histologic manifestation of human immunodeficiency virus infection included the presence of florid follicular hyperplasia (FFH) characterized by enlarged and irregularly shaped germinal centers some approximating the surface epithelium with attenuated or absence of mantle cell lymphocytes.



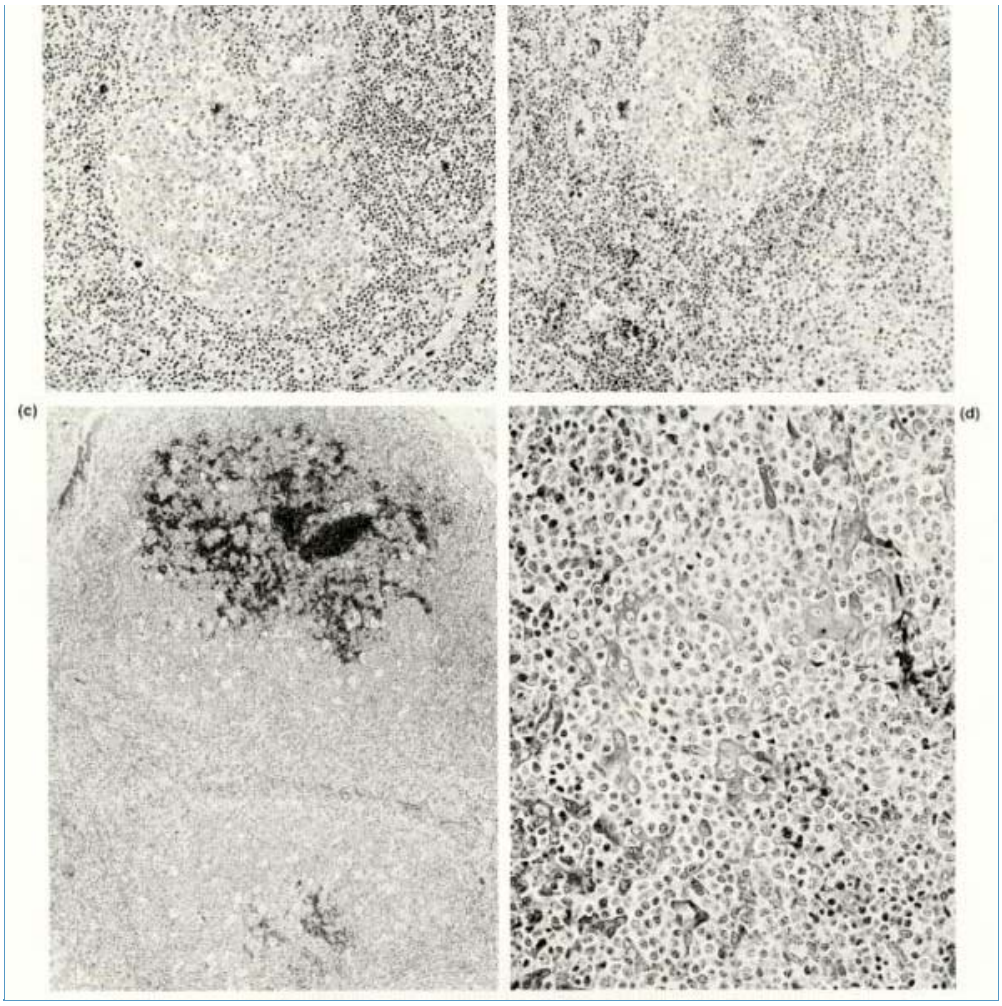
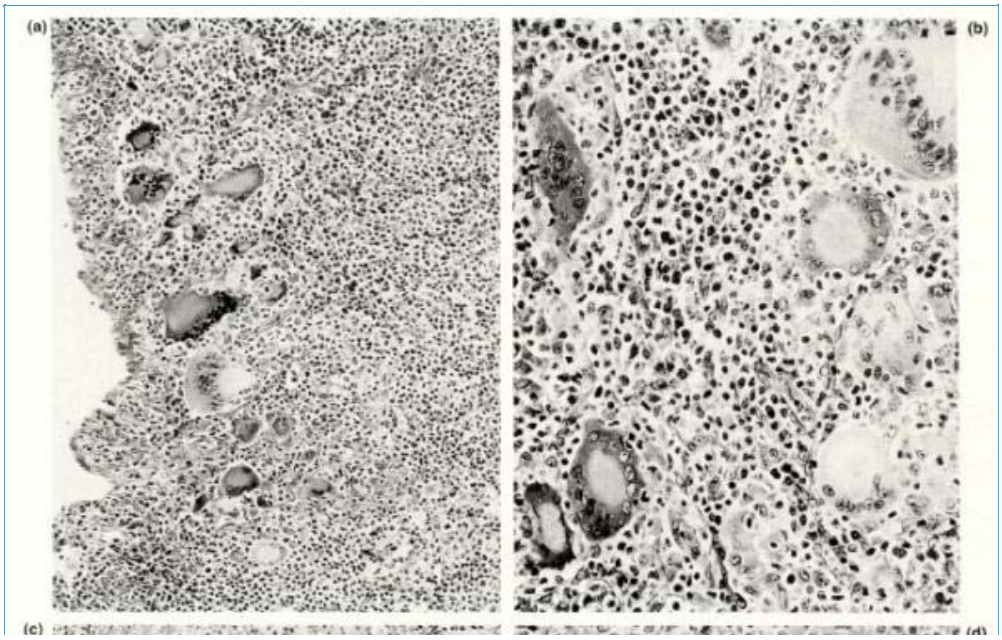


FIG. 2. Additional histologic changes suggesting early human immunodeficiency virus infection include permeation and disruption of germinal centers by "infiltrating" small lymphocytes creating a moth-eaten appearance referred to as follicle lysis **(a),** follicular involution characterized by small follicles with disappearance of the tingible body macrophages and absence of clearly defined mantle zones **(b),** intrafollicular hemorrhage **(c),** and monocytoid B-cell hyperplasia **(d).**



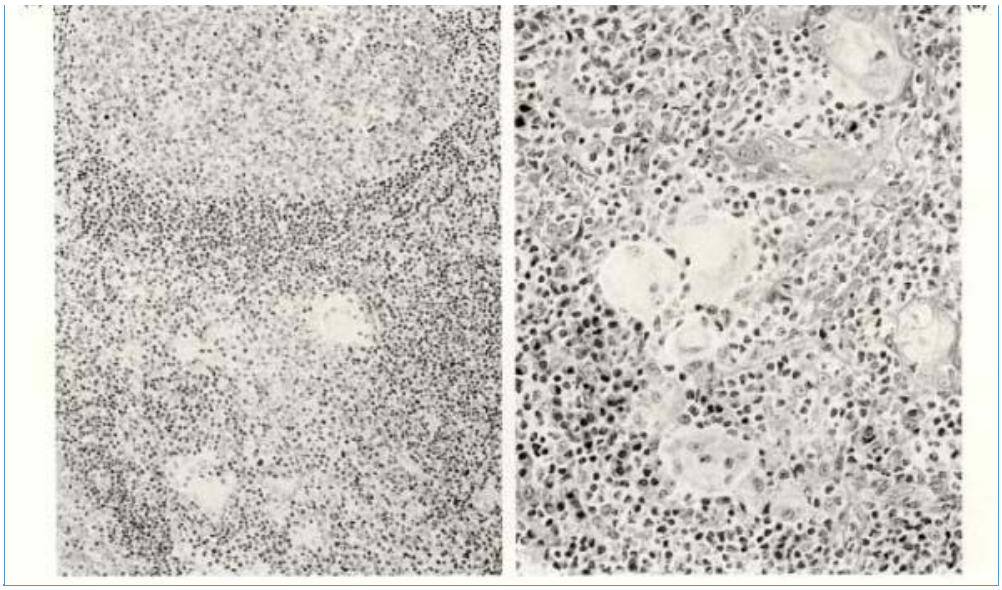
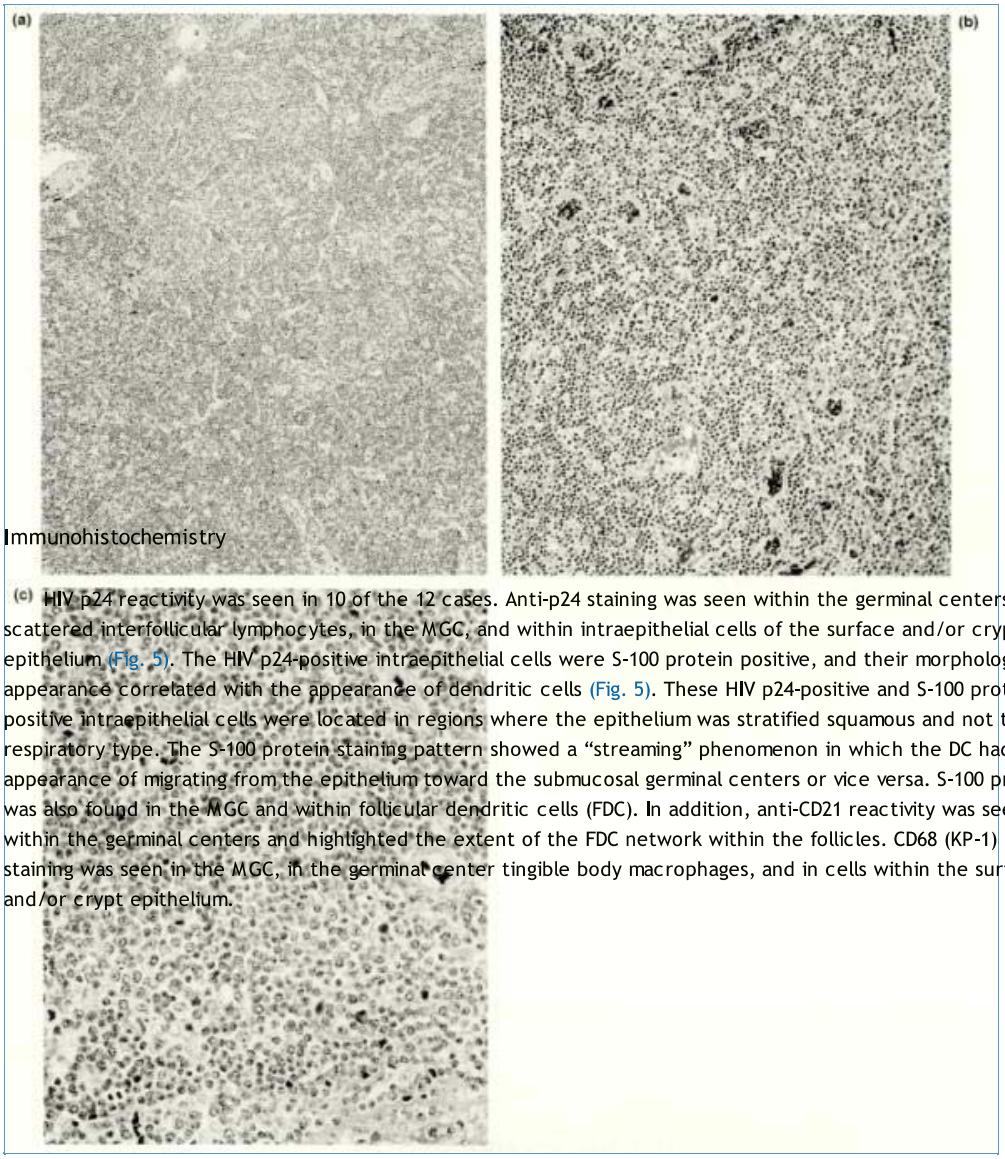


FIG. 3. Multinucleated giant cells were specific for human immunodeficiency virus infection. These giant cells varied in appearance but most commonly included cells with multiple nuclei arranged along the periphery of the cell that had a foamyappearing cytoplasm. Less often the nuclei clustered in the central portion of the cytoplasm. The giant cells characteristically localized in proximity to the surface or crypt epithelium **(a,d)** but also were identified in the intrafollicular areas **(b,c)**. In (d) the epithelial component is disrupted.

In two cases (cases 2 and 4), the histologic features contrasted with those described above and correlated with the changes seen in the terminal stages of HIV infection or AIDS. These changes included a diffuse pattern characterized by absent follicles, the presence of a dense infiltration of immunoblasts, plasma cells including Russell bodies, and mature lymphocytes varying from scattered foci to absent (lymphopenia) (Fig. 4). In addition, a pronounced fibrovascular framework was seen. In these cases, the MGC were not identified. The lymph nodes of the two patients with cervical adenopathy (cases 2 and 5) showed identical histologic changes to the corresponding adenoids. In case 2 there were changes indicative of advanced disease; in case 5 the changes reflected early infection. In all cases, special stains for microorganisms, including Gram, mucicarmine, periodic acid-Schiff, Warthin-Starry, Gomori methenamine silver, and acid fast bacilli were negative.



Immunohistochemistry

HIV p24 reactivity was seen in 10 of the 12 cases. Anti-p24 staining was seen within the germinal centers, in scattered interfollicular lymphocytes, in the MGC, and within intraepithelial cells of the surface and/or crypt epithelium (Fig. 5). The HIV p24-positive intraepithelial cells were S-100 protein positive, and their morphologic appearance correlated with the appearance of dendritic cells (Fig. 5). These HIV p24-positive and S-100 protein-positive intraepithelial cells were located in regions where the epithelium was stratified squamous and not the respiratory type. The S-100 protein staining pattern showed a "streaming" phenomenon in which the DC had the appearance of migrating from the epithelium toward the submucosal germinal centers or vice versa. S-100 protein was also found in the MGC and within follicular dendritic cells (FDC). In addition, anti-CD21 reactivity was seen within the germinal centers and highlighted the extent of the FDC network within the follicles. CD68 (KP-1) staining was seen in the MGC, in the germinal center tingible body macrophages, and in cells within the surface and/or crypt epithelium.

FIG. 4. The histologic changes of the tonsils or adenoids of patients in more advanced stages of disease were characterized by effacement of the normal architecture with absence of germinal centers **(a),** admixture of transformed lymphocytes and small lymphocytes with a prominent vascular proliferation **(b)** and intrafollicular plasmacytosis including Russell bodies **(c)**.

Reactivity with both B-cell (CD20) and T-cell markers or subsets (CD45RO, CD3, OPD4) was seen within the germinal centers and in the interfollicular regions. Intraepithelial cells also showed reactivity with CD20, CD45RB, CD3, and OPD4. The MGC showed no reactivity with either B-cell or T-cell markers. The patients in the more advanced stages of disease characterized by loss of germinal centers and a predominant plasma cell infiltrate showed a relative absence of CD45RB, CD3, or OPD4 reactive cells. In these cases, the plasma cell infiltrate showed reactivity with kappa and lambda light chains. Surface and crypt epithelia were cytokeratin reactive. There was no immunoreactivity seen with EBV-LMP, herpes simplex virus, or cytomegalovirus in any of the cases.

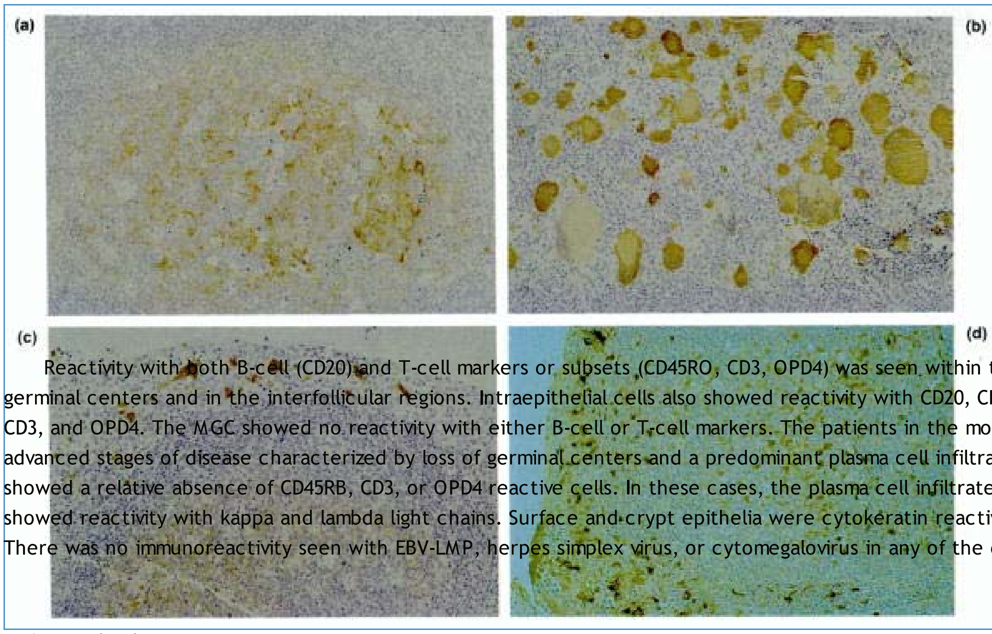
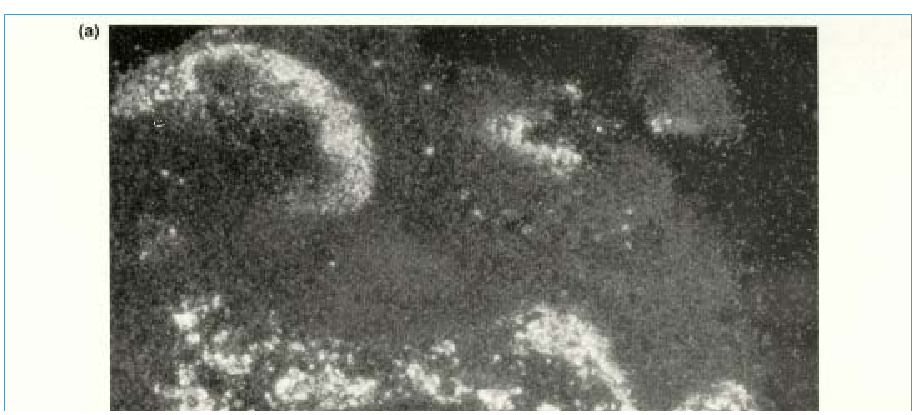


FIG. 5. Immunohistochemical reactivity included human immunodeficiency virus (HIV) p24 core antigen reactivity within follicular dendritic cells **(a)** and multinucleated giant cells **(b)**. The multinucleated giant cells reacted with S-100 protein **(c)** as well as CD68 (KP-1) (not shown). HIV p24 immunoreactivity was also present in surface epithelial cells with the morphologic appearance of dendritic cells **(d)**. The dendritic cells of the surface epithelium showed reactivity with S-100 protein **(e)**. This stain also shows these cells extending toward the subjacent lymphoid follicles.

In Situ Hybridization

In 10 of the 12 cases, there was evidence of HIV RNA by in situ hybridization. Diffuse signal was present in a follicular center cell distribution (Fig. 6). In these cases, the signal was localized primarily over the cytoplasm within the germinal centers corresponding to the follicular dendritic cell network. Scattered cells showing strong signal. These cells with the morphology of mature lymphocytes were seen within the follicles and in interfollicular and intraepithelial sites. In addition to the follicular dendritic cells and lymphocytes, strong signal was also present in the multinucleated giant cells.



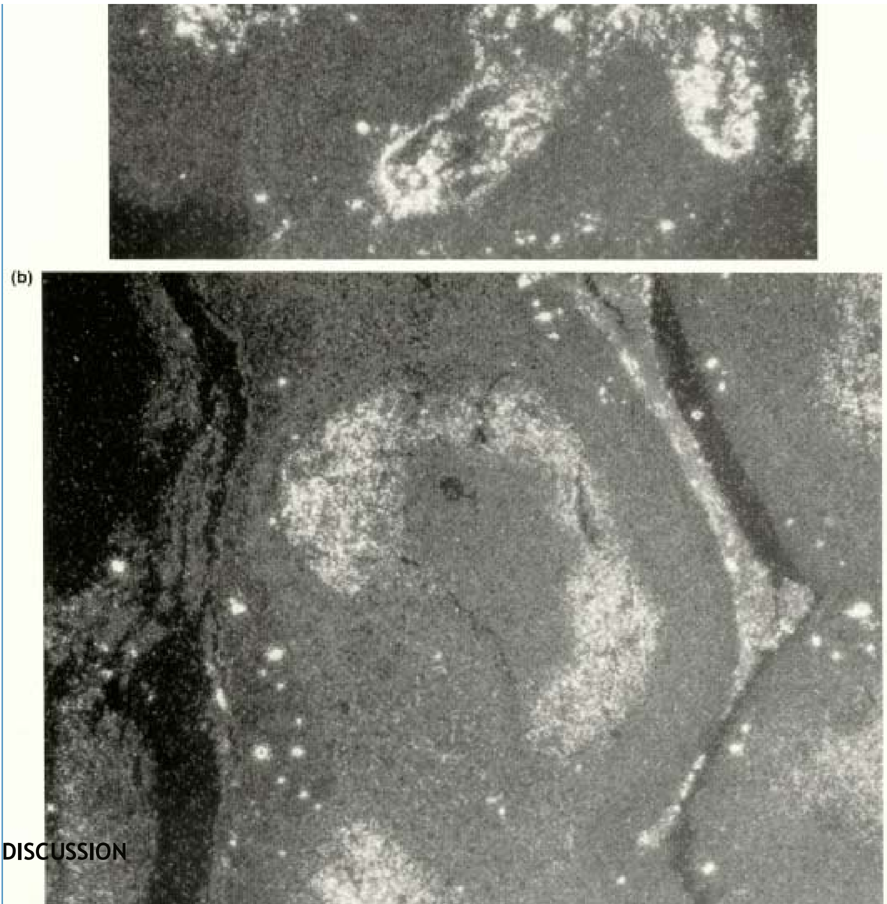

(b)

FIG. 6. In situ hybridization for human immunodeficiency virus type 1 (HIV-1) RNA using antisense riboprobe, darkfield microscopy, showing signal in a follicular dendritic pattern of staining as well as an eccentric pattern of staining in several enlarged and irregularly shaped or fused germinal centers; signal is also present in scattered interfollicular cells that included multinucleated giant cells **(a)**. Signal is seen in two germinal centers, one with eccentric staining and the other with a follicular dendritic pattern of staining; in addition, signal is also present in cells within the epithelium, in giant cells approximating the epithelial layer, and in scattered submucosal and/or interfollicular cells (b).

DISCUSSION

HIV infects peripheral blood cells, including lymphocytes (14,25), monocytes/macrophages (14,15,29,33), and dendritic cells (40) with subsequent hematogenous distribution of the virus throughout the body. A prime target site of the infected cells are the lymphoid tissues. Following HIV infection, the infected peripheral lymphocytes, monocytes/macrophages, and dendritic cells are believed to present the virus to lymph nodes throughout the body, leading to a series of irreversible morphologic changes. The morphologic changes seen in affected lymph nodes and peripheral lymphoid tissues represent a continuum that varies with the duration and progression of disease (75). The most consistent and reproducible alterations seen in lymph nodes relate to the germinal centers (49,59). The light microscopic changes induced by HIV infection follow a progressive course, from florid follicular hyperplasia in the early phases of infection followed by follicular involution and, in the end stages of AIDS, complete effacement of nodal architecture with absent germinal centers and replacement by immunoblasts and plasma cells (75).

The HIV-associated morphologic changes are not restricted to nodal tissues but also affect extranodal lymphoid tissues, such as in Waldeyer's tissue as well as the thymus (1,8,62,69). The spectrum of histopathologic changes in the adenoids and tonsils depicted in this study are identical to those described in the lymph nodes of patients infected with HIV (4,16,31,75). In conjunction with the spectrum of changes of the germinal centers and interfollicular regions, the presence of MGC in the tonsillar and adenoidal was a key diagnostic feature. The MGC were identified in the interfollicular regions, rarely within germinal centers, but the most characteristic localization of the giant cells was in proximity to surface or crypt epithelium, a feature that may correlate with HIV transmission (see below). For unexplained reasons, the MGC preferentially localized to areas in which stratified squamous epithelium (surface or crypt) was seen but not to areas in which the ciliated respiratory epithelium was present. The MGC had some resemblance to the Warthin-Finkeldey giant cells of measles. There is, however, a morphologic difference between the MGC seen in the our cases and the giants cells originally described by Finkeldey (19) and Warthin (71). The majority of the giant cells seen in our study had peripherally located nuclei and not the central, mulberry-like clustering of the nuclei as seen in the classic Warthin-Finkeldey giant cells (19,71). Therefore, the MGC are not referred to as Warthin-Finkeldey-like.

Are the multinucleated giant cells pathognomonic for tonsillar/adenoidal HIV infection? In our cases, the MGC were readily apparent in all of the patients in the early stages of HIV infection (cases 1, 3, and 5-12) but were absent in those patients who were in more advanced stages of disease (cases 2 and 4). The findings of giant cells in the early stages of disease and their disappearance in the latter stages would be expected. As the disease progresses, there is marked immune compromise and an inability to mount an effective immune response in the

face of infection. It should be noted that three cases we did not include in this study showed light microscopic features in enlarged tonsils or adenoids that suggested the possibility of early HIV infection. In these tissue specimens, there was florid follicular hyperplasia and follicle lysis. Not one of these cases, however, had associated MGC. Attempts to identify the presence of HIV by immunohistochemistry and in situ hybridization failed, and serologic evaluation for HIV infection proved negative. Extensive follow-up has failed to identify a specific cause for the enlarged tonsils and adenoids in these patients who remain disease free. The morphologic changes seen in these patients are attributed to a nonspecific reactive process. Whereas the morphologic changes associated with HIV lymphadenopathy are reproducible and have engendered histopathologic grading schemes felt to be prognostically significant (4,7,11,49,50,55), both the specificity of the light microscopic changes and the validity of these changes as prognostic indicators have been questioned (48,67). Neither of these two independent groups (48,67) found any statistically significant histologic features that predicted HIV-related adenopathy. These authors independently arrived at the conclusion that on the basis of histology alone without correlation to the clinical setting, these histologic changes could not be used in diagnosing HIV infection (48,67). In our experience, however, if MGC are added to the other histologic features, then a diagnosis of HIV infection becomes highly suspicious but still requires confirmation by adjunct studies. Similar multinucleated giant cells have been identified in lymph nodes (75) and the central nervous system (5,23,36,61,63,64,70). An important component of the histopathologic changes seen in HIV encephalitis are the MGC (61), where they may occur as part of the cellular admixture of the so-called microglial nodule, a cardinal feature of CNS AIDS, or they may appear in isolated clusters (61). Sharer et al. were the first to stress the importance of the MGC in the diagnosis of HIV encephalitis (63), and some authors have cited their paresence as characteristic for HIV encephalitis (5,63,64); however, documented cases of HIV-infected patients have been reported in which MGC were absent (5,61,63). In fact, Shahab and colleagues did not find any giant cells in their study of HIV-infected patients with enlarged nasopharyngeal lymphoid tissue (62). Therefore, neither florid follicular hyperplasia, with or without follicle lysis, nor MGC as independent (noncoexistent) findings are pathognomonic for HIV infection. We believe that finding florid follicular hyperplasia (with or without follicle lysis), together with the MGC, represents histologic features that are virtually diagnostic for HIV infection. However, confirmation by immunohistochemical, in situ hybridization or serologic testing is still required.

The clinical spectrum of HIV infection includes three phases: early or acute, latent or chronic, and crisis or final (51). The morphologic changes described above parallel the course of HIV infection. In the early stages of disease, the florid follicular hyperplasia of lymphoid tissues results in enlargement of the affected sites, which not only causes lymphadenopathy but results in enlarged adenoids or tonsils that may cause airway obstruction and raise the clinical concern for neoplastic involvement of these sites (62). Similar to the lymphoid tissues changes that occur with the progression of disease, identification of HIV also changes over time. In nodal tissues, the FDC of the germinal centers have been shown to be reservoirs of HIV RNA (3,21,59). The FDC entrap HIV allowing for presentation of the virus to competent immune cells (51). With progression of disease and continued immune suppression, the germinal centers involute and then disappear, and the reservoir of HIV RNA also disappears (21). The eventual loss of germinal centers are thought to result from destruction of the FDC network of the germinal centers (51). With destruction of the FDC there is release of HIV, accounting for increased viremia in the advanced stages of disease (51).

The two types of dendritic cells include FDC found in germinal centers and the bone marrow-derived dendritic cells (68). FDC retain native antigens as immune complexes on their cell surface and present native antigen to B cells. The bone marrow-derived dendritic cells, referred to as interdigitating dendritic cells (IDC), migrate from blood or afferent lymph to the T-dependent regions of peripheral lymphoid tissues (68). The IDC process antigens into immunogenetic peptides and present these to T cells (60). Hart and McKenzie isolated and phenotypically characterized human tonsillar dendritic and showed that these cells belong to the hematopoietic cell lineage of dendritic cells (26). In addition to T helper cells and monocytes/macrophages, dendritic cells are infected by HIV (42,43,53,54). The major reservoir for HIV type 1 is the follicular dendritic cell network of the germinal centers (21,66). The sequestration of HIV-1 by the FDC network most likely represents extracellular antigen that was retained as antibody-coated virions on the surface of the FDC and not active infection of the FDC (52). The bone marrow-derived IDC also are infected by HIV (42,43,53,54). However, there has been conflicting data in the literature with regard to infection, depletion and dysfunction of dendritic cells in HIV-infected individuals (9,35,56). Recently, Weissman et al. (73) showed that there are three populations of cells with dendritic morphology in peripheral blood, only one of which is infectable with HIV-1. These authors found that all three populations of dendritic cells expressed CD4 but that the type infected by HIV-1 was the only one that did not share the same T-cell stimulatory activity. Our findings confirmed the presence of HIV extracellularly as retained virus in the FDC network of adenoidal and tonsillar germinal centers. Consistently intense anti-HIV p24 core antigen reactivity was identified within the germinal centers, and in situ hybridization studies showed concentration of signal in the follicular dendritic cell network. As shown by Fox et al., with advancing disease this reservoir disappears as the germinal centers involute (21), which would explain the cases in this study that failed to show immunoreactivity for HIV p24 or signal for HIV RNA by in situ hybridization. These patients were known to be HIV infected and were in a more advanced stage of disease. These findings also correlate with the presence of

antibodies directed against the core antigen (anti-p24) in the serum of infected patients. Plasma viremia is highest in the early and late stages of disease (11-13,18,51). Anti-p24 response is greatest in the clinical latent phase of infection, at which time HIV p24 antigen levels decline. Anti-p24 levels remain elevated until the late phase of disease but eventually decline to undetectable levels (51). Despite the absence of detectable HIV p24 antigen in the clinical latent phase, the virus is sequestered and is still present within the FDC network of lymphoid tissues (51). The most compelling evidence to support the ongoing presence and proliferation of HIV is the fact that CD4+ T-lymphocyte cell counts progressively decline over this period in spite of serologically undetectable virus.

In addition to the FDC, another pool of virus as identified by HIV p24 immunoreactivity and HIV-RNA in situ hybridization was within (intracellular) mucosal dendritic cells, scattered lymphoid cells, and MGC. Localization of HIV by electron microscopy, immunohistochemistry, and in situ hybridization has been seen in the MGC of HIV encephalitis as well as in intracerebral macrophages and activated neuroglial cells (61,64). It should be noted that HIV and cytomegalovirus coinfected MGC have been reported in cytomegalovirus encephalomyeloradiculitis and HIV encephalitis (2). We did not identify any instances in this study in which the MGC were coinfected with HIV and cytomegalovirus. Burke and colleagues in two separate studies (6,7) could not immunophenotype the syncytial giant cells seen in HIV-infected patients. Similarly, we could not substantiate any specific lineage immunophenotypic expression in the MGC. In HIV encephalitis, the infected intracerebral cells have been shown to be CD4 positive, as are the helper T-cells used by the HIV virus as a binding site (61). These findings would confirm T-cell deviation of the MGC associated with HIV infection and explain their capacity to harbor and disseminate the virus; however, the presence of HIV-1 in gut mucosal cells has been reported (20,27,47), and in vitro studies by Yahi et al (76) have shown that HIV-1 can directly infect intestinal cells via a CD4-independent mechanism mediated by galactosyl ceramide receptor. The findings in our study may support HIV infection of the adenoids and tonsils mediated via both CD4-dependent and CD4-independent mechanisms (see below).

The mechanism of giant cell (syncytia) formation in AIDS patients has been investigated by Lifson et al. (41), who showed that in vitro giant cell formation resulted via cell fusion of CD4-positive cells, that antibody to CD4 specifically inhibited fusion, and that uninfected CD4-negative cells (in contrast to uninfected CD4 positive cells) did not undergo syncytium formation (41). The origin of these MGC in vivo have not been determined, however. In our study, the MGC were reactive with the CD68 (KP-1) as well as with S-100 protein. Although macrophages do not react with S-100 protein, dendritic cells not only show S-100 protein reactivity but may also express CD68 reactivity (personal communication, R.M. Steinman). Therefore, whereas the histogenesis of the MGC appears to include dendritic cells, the formation of the MGC does not appear to include a component of macrophage derivation. In support of this contention, Frankel and colleagues have shown that the MGC of HIV-infected adenoids reacted with both S-100 protein and with the dendritic cell marker p55 (22). These authors postulate that in the presence of HIV-1 infection, the MGC may represent the interaction of dendritic cells and T-cell lymphocytes. During infections of dendritic cell-lymphocyte cell mixtures in culture, the syncytial cells are the principal sites in which viral p24 antigen and budding virions are found (58).

HIV infects and ultimately depletes CD4-positive T-helper cells using the CD4 protein as a receptor for infection of susceptible cells (32). Monocytes also express CD4, however, and can be infected by HIV via this cell-surface molecule (65). Both CD4-positive T-lymphocytes and monocyte/macrophages play an important role in the interaction and propagation of HIV infection (33). These cells are implicated as major targets by the HIV, serving as reservoirs for HIV and as vehicles in dessemination of the virus (14,15,65). Through hematogenous spread, the HIV-infected CD4-positive lymphocytes and monocytes could introduce the virus to the tonsillar and adenoidal germinal centers, where FDC entrap the virus. The FDC may then transmit infection to various cells as they migrate through lymphoid germinal centers (14). IDC can carry and transfer HIV-1 to T cells. Given these facts, HIV may be brought to the tonsils and adenoids via the blood by infected peripheral blood T-lymphocytes, monocytes/macrophages, and dendritic cells. As previously discussed, our findings confirmed the presence of anti-HIV p24 core antigen reactivity in the FDC network of the germinal centers and in the T-cell-dependent regions of the interfollicular areas, which would corroborate hematogenous spread of HIV to the tonsils and adenoids. An alternative route of tonsillar and adenoidal HIV infection is via transmucosal infection of the tonsils and adenoids. Transmucosal HIV infection has been suggested in relationship to the other mucosal sites (45), and HIV-1 has been identified within mucosal cells of the cervix (57) and the gastrointestinal tract (20,27,47),77).

Relative to our cases, several findings strongly support transmucosal infection. Interdigitating dendritic cells, as described above, are identified in the T-cell-dependent regions of peripheral lymphoid tissues but are also found in skin and mucous membranes (59,68). In cutaneous sites, nonlymphoid dendritic cells (Langerhans' cells) are found in the epithelium (68). Antigen-bearing dendritic cells from cutaneous sites have been shown to migrate from the skin following contact sensitization and migrate to regional lymph nodes (28,37,38). Further, Langerhans' cells migrate as so-called veiled cells via the afferent lymphatics to the T-dependent region of lymph nodes

cells migrate as so-called veiled cells via the afferent lymphatics to the T-dependent region of lymph nodes, where they differentiate into antigen-presenting interdigitating dendritic cells (53,54). Pope et al. (58) reported that conjugates of dendritic cells and memory T lymphocytes from skin facilitate the production of infection with HIV-1. This finding is further supported by the findings of Cameron et al. (10), who showed that a critical variable for productive HIV infection of dendritic cells was a required interaction with CD4+ T-cells. Among the dendritic cells analyzed by these authors were those of tonsillar origin. In this way, dendritic cells found in oral, anal, vaginal, and cervical mucous membranes as well as the upper aerodigestive tract (i.e., tonsils and adenoids) may be directly infected by HIV via sexual transmission. In theory, following infection, tonsillar and adenoidal mucosal dendritic cells carry the virus from the epithelium to the germinal centers, resulting in infected FDCs. Several of our findings support this concept. First, S-100 protein, a marker of many cells, including dendritic cells, was present within intraepithelial dendritic cells, which were “migrating” or steaming toward the germinal centers. Next, anti-HIV p24 immunoreactivity was identified within the epithelial layers and, specifically, was seen in cells with the morphologic appearance of dendritic cells. As we have shown, a consistent finding in those patients who were in the early stages of disease and were still immunocompetent, was the presence of MGC with localization to the tonsillar and nasopharyngeal epithelium. This specific localization is difficult to understand except in the context that the HIV-infected mucosal dendritic cells, representing potent antigen-processing cells (68), generated an immune response in the form of the multinucleated giant cells. In this way, the host is reacting to theprimary site from which the antigen is being presented to that specific tissue. It would make less sense to postulate that the virus is being introduced entirely via the germinal centers, for if that were true, then the giant cells should preferentially congregate within or around the germinal centers, which they did not. Finally, the tonsillar and nasopharyngeal mucosal epithelium typically includes the presence of lymphocytes (lymphoepithelium) that are primarily of B-cell lineage but also includes T-cells as well as macrophages (46). Our immunohistochemical evaluation showed both B cells and T cells within the epithelia of the tonsils and adenoids. If, as Pope et al. have documented (58), conjugates of dendritic cells and memory T lymphocytes are required to facilitate the production of HIV infection, then the presence of T lymphocytes within the tonsillar and adenoidal epithelium would support this finding. The clinical findings of the patients in this study also lend support for transmucosal infection. The patients in the early phases of infection had disease limited to the nasopharynx and tonsils but did not have generalized lymphadenopathy. If the virus was preferentially brought to the tonsils and adenoids via the blood, why would there be selective enlargement of these structures in the absence of the progressive generalized lymphadenopathy seen in early or subacute HIV infection? This is further supported by the findings of Pantaleo et al. (52), who documented the presence of high levels of HIV in early stage disease in both lymph nodes and lymphoid tissues other than lymph nodes such as adenoids and tonsils. Their findings were an indication that there was systemic dissemination of HIV among lymphoid tissues and not localization to lymph nodes. In fact, Pantaleo et al. state that all the lymph nodes they obtained from patients in early stage disease had follicular hyperplasia (52). Therefore, we believe it is reasonable to assume that the patients in our study probably had disseminated disease and probably had some degree of nodal-based follicular hyperplasia that, at the time of adenoidal or tonsillar enlargement, was subclinical (absence of generalized lymphadenopathy). Two of the patients did have cervical adenopathy but no evidence of progressive generalized lymphadenopathy. Perhaps this is indicative of a second “hit” by the virus, accounting for the preferential enlargement of these sites in the absence of adenopathy.

Admittedly, we cannot unequivocally determine the direction of events, but two mutually inclusive routes of infection are suggested. The first would be hematogenous spread via infected peripheral blood cells with subsequent delivery to lymphoid tissues throughout the body. The second would be by direct infection of the mucosa of the upper aerodigestive tract. The upper aerodigestive tract mucosa represents part of the common mucosal immune system (44), which can be divided into sites where antigen is encountered and initial responses are induced (inductive sites) and sites where IgA plasma cells and cytotoxic T lymphocytes are found and where the production of secretory IgA antibodies results in local immune protection (effector sites) (45). The upper aerodigestive tract, including the tonsils and adenoids, may serve as either an induction or effector site (45). HIV, serving as the antigen, is presented to the FDC network of the adenoids or tonsils by infected circulating blood cells. Alternatively, or perhaps simultaneously, HIV presentation directly to the mucosal surface effects a local adenoidal or tonsillar immune response. The latter route of infection would be akin to the non-parenteral administration of vaccines (antigens) used in achieving immunity through the common mucosal immune system (44).

We present 12 patients with enlarged adenoids or tonsils that were clinically suspicious for a neoplasm. Based on the morphologic changes, HIV infection was suspected even in asymptomatic patients. Immunohistochemical, in situ hybridization, and serologic evaluation confirmed the presence of HIV infection in all of the patients. Consistent and reproducible histologic features in the early/subacute stages of disease were florid follicular hyperplasia and MGC. The MGC preferentially localized to surface or crypt stratified squamous epithelium and were typically absent in patients who were in the advanced stages of disease. The MGC may represent syncytia of infected T lymphocytes and activated dendritic cells, but this is speculative. Our findings distinguish two pools of HIV: extracellularly within the germinal center FDC network of the adenoids and tonsils and intracellularly in the multinucleated giant cells and mucosal dendritic cells. A critical question that remains unanswered is how the virus got to this area. Our findings suggest the possibility of a “double hit” phenomenon: one route via the blood

with HIV-infected circulating T lymphocytes, monocytes/macrophages, and dendritic cells delivering the virus to these extralymphoid structures; the other route via transmucosal infection in which infected circulating T cells come into contact with and infect activated intraepithelial dendritic cells with subsequent presentation of the virus to the germinal centers and the T-cell dependent regions.

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Key Words: HIV; AIDS; Adenoids; Tonsils; Immunohistochemistry; In Situ Hybridization; Multinucleated giant cells; Dendritic cells; Mucosal immunity

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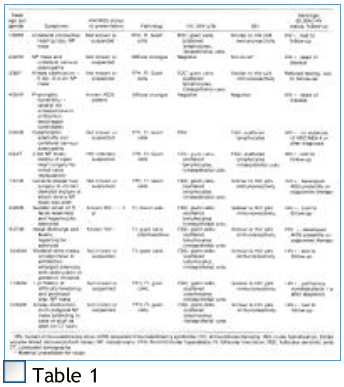
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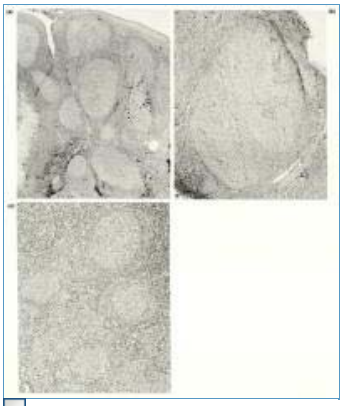
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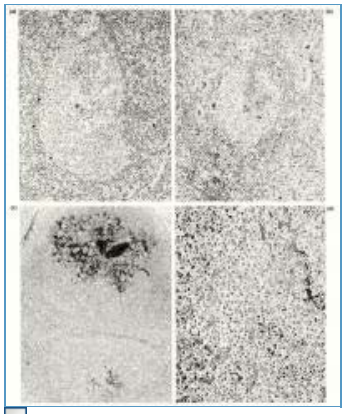
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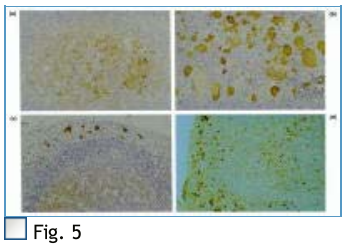
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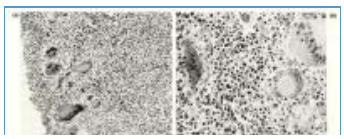

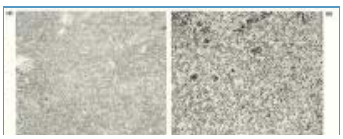

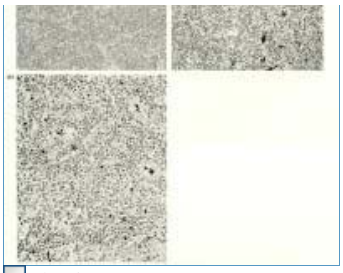

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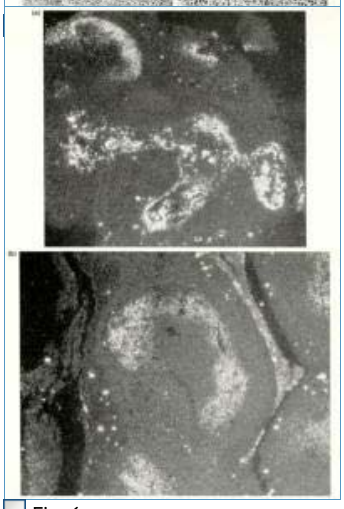

Fig. 6

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