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Spectrum of Morphological Changes in Lymph Nodes of HIV Infected Patients with Lymphadenopathy

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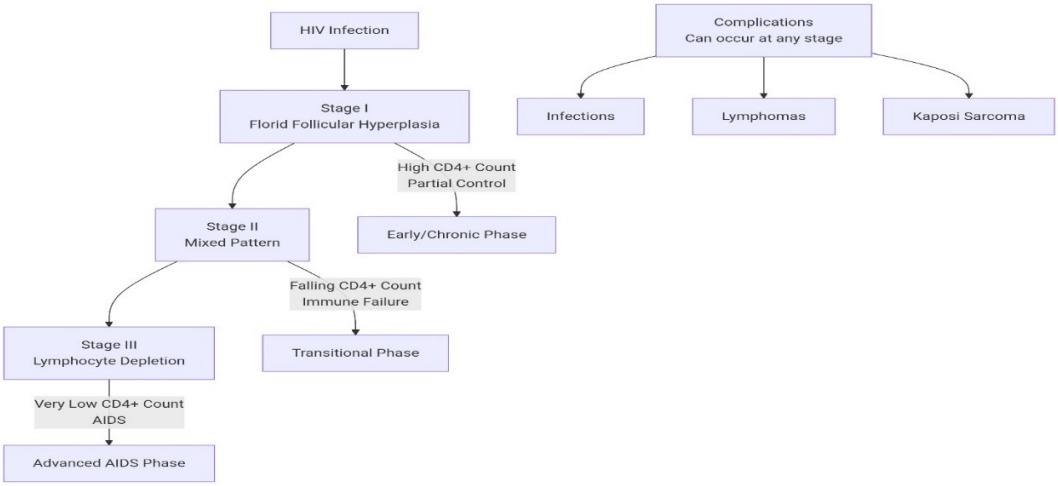
Abstract:
Lymphadenopathy is a cardinal clinical feature of HIV infection, reflecting the complex and dynamic interplay between the virus and the host immune system. The morphological changes within the lymph node are not static; they evolve through predictable histological stages that mirror the progressive immunological decline. This review systematically details the spectrum of pathological findings, from the initial florid reactive hyperplasia of early infection to the profound lymphocyte depletion of advanced AIDS. Understanding this spectrum is crucial for accurate diagnosis, as the lymph node architecture provides a histological roadmap of disease progression and is a common site for opportunistic infections and neoplasms.

Keywords: HIV, Lymphadenopathy, Lymph Node, Morphology, Histopathology, Follicular Hyperplasia, Lymphocyte Depletion, AIDS, Opportunistic Infections, Lymphoma

1. Introduction:
Human Immunodeficiency Virus (HIV) primarily targets the immune system, with CD4+ T-lymphocytes and lymphoid tissue serving as the major reservoirs. Lymphadenopathy, therefore, is a near-universal finding throughout the infection course[2]. The histological evolution in lymph nodes directly parallels the virological and immunological status of the patient, transitioning from intense immune activation to eventual collapse. Pathologists must be familiar with this spectrum to distinguish benign reactive patterns from specific infectious or neoplastic complications.

The evaluation of lymph node morphology has been one
Approach to diagnosis and in understanding the nature of the
Immune dysfunction in these condition

The following chart outlines the core histological progression and its clinical correlates:



2. The Pattern-Based Classification of HIV-Related Lymphadenopathy

The morphological changes can be categorized into three main patterns, which often represent a chronological sequence.

2.1 Pattern I: Florid Follicular Hyperplasia (Early/Chronic Phase)

This pattern is characteristic of the early and clinically latent phases, where partial immune control remains.

Architectural Changes:

- Marked Follicular Hyperplasia: The cortex is expanded by an increased number and size of reactive germinal centers. These follicles are often irregularly shaped ("geographic" or "serpiginous").
- **Follicle Lysis:** A hallmark feature. Germinal centers become infiltrated by small lymphocytes, capillaries, and dendritic cells, leading to fragmentation and disruption of the mantle zone. This is due to an influx of CD8+ T-cells and polyclonal B-cell activation.
- **"Burnt-Out" Follicles:** Follicles may appear pale and expanded due to a proliferation of follicular dendritic cells (FDCs) and deposition of hyaline material.

2.2 Pattern II: Mixed Pattern

- Clinical Correlation: This is a transitional phase seen as the CD4 count falls (200-500 cells/μL), signaling the beginning of significant immune failure and progression towards AIDS.
- Key Morphological Features:
- Follicular Involution: The reactive germinal centers shrink and disappear.
- Paracortical Expansion: The paracortex remains hyperplastic, becoming the dominant component.
- Scattered "Burned-Out" Follicles: Remnants of follicles are seen as hyalinized scars.
- General Disorganization: The clear distinction between cortical and paracortical areas is lost.

2.3. Pattern III: Lymphocyte Depletion

- Clinical Correlation: This pattern is characteristic of full-blown AIDS in untreated patients, with very low CD4 counts (<200 cells/μL). It reflects a "burnt-out" lymph node incapable of mounting an effective immune response.
- Key Morphological Features:
- Profound Lymphocyte Loss: The node is hypocellular, small, and often fibrotic.
- Absent Follicles: No reactive germinal centers are found.
- Hyalinization and Fibrosis: The normal architecture is replaced by pink, acellular hyaline material and collagen.
- Vascular Prominence: Blood vessels may appear more prominent against the depleted background.

Discussion:

Lymph node biopsies are frequently done in HIV positive Patients. In the course of AIDS, a lymph node biopsy may Elicit the cause of the lymphadenopathy or provide the Etiologic diagnosis of a systemic disease. Tourneau et al. Have remarked on the importance attached to lymph node Biopsy evaluation in HIV individuals in his article. Suggested that the light microscopic features with detail Examination are very suggestive of AIDS. 8 Harry et al explored the histologic features of lymph Node biopsy of 79 HIV positive patients and found three Histological patterns. 9

1. Follicular hyperplasia with cytolysis.
2. Follicular involution with hyper vascularity.
3. Combination of the 1 and 2.

with follicular hyperplasia with cytolysis were Noted to have better prognosis than other two. So these Workers opined that the all histological patterns represent Stages of progression in HIV infection. Similar observations Were also made by H J C Rashleigh Belcher et al. 10The most Common his topathological changes seen are Mainly due to the regionreactivity. This is expressed by

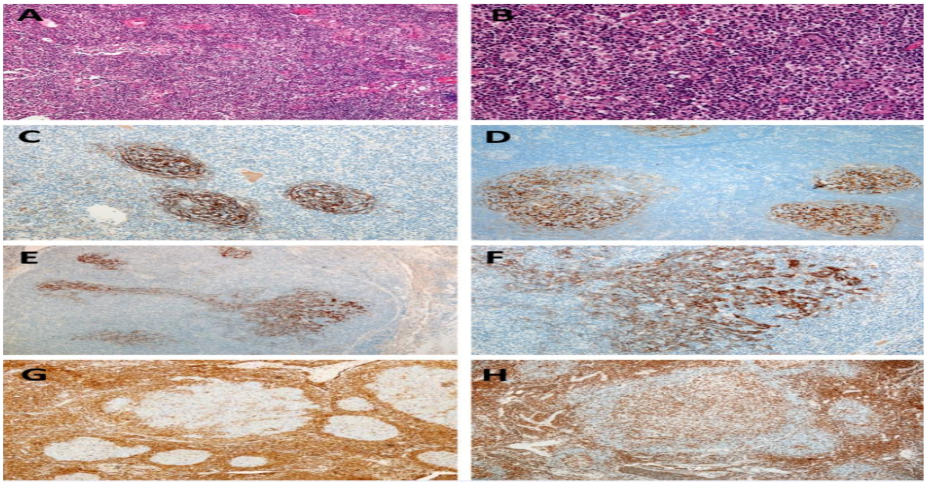


Fig. 1: Reactive lymphadenitis. A): Follicle with mantle zone hyperplasia. (H&E 10X); b): Follicle lysis (H&E 10X), c): Showing hyaline sation within arterioles of geminal center (H&E 20X);d): Monocytoid cells(H,&E 20X)

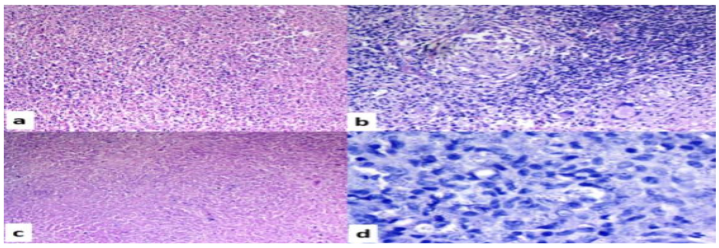


Fig. 2: Tuberculosis lymphadenitis; a): Neutrophillic microabscess with granular debris (H&E 10X); b): Granulomas (H&E 10X); c): Caseous necrosis (H&E 10X); d): Histiocyt

Lymph node compartment	**Morphological features**	**No. of cases (%)**
	Size of follicles (Large)	**13 (36.1)**
Germinal center	Follicle lysis	**27 (75)**
	Mantle zone effacement	**14 (38.9)**
	Hemorrhage	**4 (11.1)**
	Endothelial cells	**36 (100)**
Para cortex	Para cortex expansion	**17 (47.2)**
	Dermatopathic features	**16 (44)**
	Monocytoid cells	**13 (36.1)**
Sinuses	Sinus histiocytosis	**3 (8.3)**
Others	Plasmacytosis	**13 (36.1)**

Table 1: The various histopathologic features evaluated in these cases are shown Morphologic features (n=36) Reactive changes es filled with histoplasma (H&E 40X)

Pattern	No. Of cases	Percentage %
Table A	**8**	**22.2**
Table B	**28**	**77.8**
Table c	**0**	**0**

Table 2: HIV lymphadenopathy- Type of pattern. (n=36)

3.Specific Pathological Complications within HIV Lymphadenopathy

Beyond these reactive patterns, lymph nodes are common sites for specific pathologies that can cause or exacerbate lymphadenopathy.

- **Infections (Opportunistic and Co-infections):**

  Mycobacterial Infections:

  Mycobacterium avium-intracellulare (MAI) is common, causing poorly formed granulomas with abundant foamy histiocytes packed with acid-fast bacilli. Tuberculosis may cause caseating granulomas.
- **Fungal Infections:** Histoplasmosis, Cryptococcosis, and Coccidioidomycosis can cause granulomatous inflammation or histiocytic infiltrates.
- **Viral Infections:** Cytomegalovirus (CMV) inclusions; Kaposi Sarcoma Herpesvirus (KSHV/HHV-8).
- **Lymphomas**:

  HIV-associated lymphomas are typically high-grade B-cell neoplasms. The most common is Diffuse Large B-Cell Lymphoma (DLBCL), often with a centroblastic or immunoblastic morphology. Burkitt Lymphoma is also significantly increased in incidence. Primary Effusion Lymphoma and Plasmablastic Lymphoma are strongly associated with KSHV and EBV, respectively.
- **Kaposi Sarcoma (KS):**

  Characterized by slit-like vascular spaces, spindle cells, extravasated red blood cells, and hyaline globules. Driven by KSHV/HHV-8.

4.Differential Diagnosis

The histological patterns must be distinguished from other causes of lymphadenopathy:

- **Florid Follicular Hyperplasia (Pattern I):** Must be distinguished from Castleman disease (especially the hyaline-vascular and plasma cell types), syphilis, and other viral infections (EBV, CMV).

- **Lymphocyte Depletion (Pattern III):** Can resemble Hodgkin Lymphoma (especially the nodular sclerosis subtype with lymphocyte depletion) or changes post-chemotherapy/radiotherapy

The presence of any mass-forming lesion or necrosis should always raise suspicion for lymphoma or mycobacterial infection, respectively.

- **Complications Overlaying the Spectrum**

At any point in this spectrum, but especially in the Mixed and Depletion stages, the immunosuppressed environment allows for other pathologies to manifest in the lymph nodes.

A. Opportunistic Infections

The depleted immune system cannot control pathogens that a healthy person could easily clear.

Mycobacteria: Mycobacterium avium-intracellulare (MAI) causes diffuse infiltrates of foamy histiocytes packed with acid-fast bacilli. Mycobacterium tuberculosis causes caseating granulomas.

Fungi: Histoplasmosis, Cryptococcosis, and Coccidioidomycosis can cause granulomatous inflammation or histiocytic infiltrates.

Viruses: Cytomegalovirus (CMV) shows characteristic viral inclusions.

Bacteria: Bartonella henselae/quintana causes bacillary angiomatosis, with lobular vascular proliferations and neutrophilic debris.

B. Neoplasms

HIV-associated immunosuppression dramatically increases the risk of certain cancers.

Lymphomas: These are typically aggressive B-cell lymphomas.

Diffuse Large B-Cell Lymphoma (DLBCL): The most common HIV-associated lymphoma.

Burkitt Lymphoma: High-grade with a "starry sky" appearance.

Plasmablastic Lymphoma: Often associated with Epstein-Barr Virus (EBV).

Kaposi Sarcoma (KS): Caused by Human Herpesvirus-8 (HHV-8). Histology shows spindle-shaped tumor cells forming slit-like vascular spaces, extravasated red blood cells, and hyaline globules.

Treatment of HIV:

HIV (Human Immunodeficiency Virus) is transmitted primarily through **unprotected sex**, **sharing contaminated needles**, and **from mother to child** during pregnancy, childbirth, or breastfeeding. Prevention focuses on reducing exposure to the virus and strengthening protective behaviors.

Goals of HIV Treatment:

Achieve and maintain viral suppression → HIV RNA <50 copies Restore/preserve immune function → Increase CD4 count

Reduce HIV-related morbidity and mortality

Prevent transmission ("U = U": Undetectable = Untransmittable)

ART is lifelong, started as soon as HIV is diagnosed, regardless of CD4 count.

Principles of Antiretroviral Therapy (ART):

ART uses a combination of at least 2–3 active drugs from different classes to:

1. Block multiple stages of HIV replication
2. Prevent drug resistances .
3. Achieve durable viral suppression.
4. Modern regimens are typically one pill once.
5. Modern regimens are typically one pill once daily.

Major Classes of Antiretroviral Drugs

1.NRTIs – Nucleoside/Nucleotide Reverse Transcriptase Inhibitors

Backbone of most regimens (usually 2 drugs).

Common drugs:

Tenofovir disoproxil fumarate (TDF)
Tenofovir alafenamide (TAF)
Emtricitabine (FTC)
Lamivudine (3TC)
Abacavir (ABC)

2.NNRTIs – Non-Nucleoside Reverse Transcriptase Inhibitors

Less commonly first-line today.

Drugs:

-Efavirenz (EFV)
-Rilpivirine (RPV)
-Doravirine (DOR)

3.INSTIs – Integrase Strand Transfer Inhibitors

Current first-line standard: potent, minimal side effects.

Drugs:

-Dolutegravir (DTG)
-Bictegravir (BIC)
-Raltegravir (RAL)
-Caterair (CAB) – long-acting injectable

4.Protease Inhibitors (PIs)

Conclusion

The lymph node in HIV infection serves as a critical barometer of disease activity. The morphological spectrum—from florid hyperplasia through mixed patterns to lymphocyte depletion—provides a histopathological correlate of the relentless viral replication and subsequent immune system degradation. A thorough histological examination, often supplemented by special stains (AFB, GMS), immunohistochemistry (for CD4, CD8, CD21, CD30, HHV-8, etc.), and molecular studies, is essential not only for staging the HIV-related changes but, more importantly, for identifying the specific opportunistic infections and neoplasms that define the clinical course of AIDS. In the modern antiretroviral therapy (ART) era, the classic Pattern III is less frequently encountered, but understanding

the full spectrum remains vital for global pathology practice.

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