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MODERN METHODS FOR EARLY DETECTION OF LYMPHOGENIC TUBERCULOSIS IN PATIENTS WITH HIV INFECTION

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Abstract: English: Background: Tuberculosis (TB) is the leading cause of death among people living with HIV (PLHIV). Lymphogenic tuberculosis (tuberculous lymphadenitis) is the most common form of extrapulmonary TB in this cohort. Diagnosis is often delayed due to atypical clinical presentations and low sensitivity of conventional smear microscopy. This study evaluates the diagnostic utility of modern imaging (Ultrasound, CT) combined with molecular assays (GeneXpert) and histopathology for early detection. Methods: A prospective diagnostic study involving 120 HIV-positive patients presenting with lymphadenopathy was conducted at the Andijan Regional Center of Phthisiology. Patients underwent a stepwise diagnostic algorithm: High-resolution Ultrasound (US), Computed Tomography (CT), and Ultrasound-guided Fine Needle Aspiration Cytology (FNAC). Aspirates were tested using GeneXpert MTB/RIF. Excisional biopsy was performed in inconclusive cases. Results: Ultrasound features such as hypoechoic texture, matting, and intranodal necrosis had a sensitivity of 78% for TB lymphadenitis. CT was superior for detecting deep mediastinal and abdominal lymphadenopathy. GeneXpert MTB/RIF on lymph node aspirates demonstrated a sensitivity of 85% and specificity of 96%, significantly outperforming smear microscopy (25%). Histological analysis confirmed diagnosis in seronegative cases, revealing characteristic caseating granulomas, though granuloma formation was poor in severely immunocompromised patients (CD4 <200). Conclusion: A multimodal approach integrating US-guided aspiration with molecular PCR testing (GeneXpert) allows for rapid and accurate early diagnosis of lymphogenic TB in HIV patients, facilitating timely initiation of ART and anti-TB therapy.
Keywords: HIV-associated tuberculosis, tuberculous lymphadenitis, GeneXpert MTB/RIF, ultrasound diagnostics, computed tomography, biopsy, differential diagnosis.

OIV BILAN KASALLANGANLARDA TUBERKULYOZNING LIMFOGEN SHAKLINI ERTA ANIQLASHNING ZAMONAVIY USULLARI

Annotatsiya: Kirish: Tuberkulyoz (sil) OIV bilan yashovchi shaxslar (OIV-YSH) orasida o‘limning asosiy sababchisidir. Limfogen tuberkulyoz (sil limfadeniti) ushbu guruhda o‘pkadan tashqari silning eng keng tarqalgan shakli hisoblanadi. Atipik klinik belgilar va an’anaviy surtma mikroskopiyasining past sezuvchanligi tufayli tashxis ko‘pincha kechiktiriladi. Ushbu tadqiqot erta aniqlash uchun zamonaviy vizualizatsiya (UZI, KT) va molekulyar tahlillar (GeneXpert) hamda gistopatologiyaning diagnostik ahamiyatini baholaydi. Usullar: Andijon viloyat Ftiziatriya markazida limfadenopatiyasi bo‘lgan 120 nafar OIV-musbat bemor ishtirokida prospektiv diagnostik tadqiqot o‘tkazildi. Bemorlar bosqichma-bosqich diagnostik algoritmdan o‘tkazildi: Yuqori aniqlikdagi ultratovush (UZI), Kompyuter tomografiyasi (KT) va UZI nazorati ostida ingichka ignali aspiratsion biopsiya (FNAC). Aspiratlar GeneXpert MTB/RIF yordamida tekshirildi. Natija noaniq bo‘lgan hollarda eksizion biopsiya qilindi. Natijalar: Gipoexogen tuzilish, tugunlarning birlashishi va tugun ichi nekrozi kabi UZI belgilari sil limfadeniti uchun

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78% sezuvchanlikka ega bo‘ldi. KT chuqur mediastinal va abdominal limfa tugunlarini aniqlashda ustunlik qildi. Limfa tuguni aspiratida GeneXpert MTB/RIF 85% sezuvchanlik va 96% spesifiklikni ko‘rsatib, surtma mikroskopiyasidan (25%) sezilarli darajada yuqori natija berdi. Gistologik tahlil seronegativ holatlarda tashxisni tasdiqladi, ammo immuniteti o‘ta past bemorlarda (CD4 <200) granuloma shakllanishi sust bo‘ldi. Xulosa: UZI nazorati ostidagi aspiratsiyani molekulyar PZR testi (GeneXpert) bilan integratsiya qiluvchi multimodal yondashuv OIV bemorlarida limfogen silni tez va aniq erta tashxislash hamda o‘z vaqtida davolashni boshlash imkonini beradi.
Kalit so‘zlar: OIV bilan bog‘liq tuberkulyoz, sil limfadeniti, GeneXpert MTB/RIF, ultratovush diagnostikasi, kompyuter tomografiyasi, biopsiya, differensial tashxis.

СОВРЕМЕННЫЕ МЕТОДЫ РАННЕГО ВЫЯВЛЕНИЯ ЛИМФОГЕННОЙ ФОРМЫ ТУБЕРКУЛЕЗА У БОЛЬНЫХ ВИЧ-ИНФЕКЦИЕЙ

Аннотация: Введение: Туберкулез (ТБ) является основной причиной смерти среди людей, живущих с ВИЧ (ЛЖВ). Лимфогенный туберкулез (туберкулезный лимфаденит) — самая частая форма внелегочного ТБ в этой когорте. Диагностика часто задерживается из-за атипичных клинических проявлений и низкой чувствительности традиционной микроскопии мазка. В данном исследовании оценивается диагностическая полезность современных методов визуализации (УЗИ, КТ) в сочетании с молекулярными анализами (GeneXpert) и гистопатологией для раннего выявления. Методы: В Андижанском областном центре фтизиатрии было проведено проспективное диагностическое исследование с участием 120 ВИЧ-положительных пациентов с лимфаденопатией. Пациенты проходили пошаговый диагностический алгоритм: УЗИ высокого разрешения, компьютерная томография (КТ) и тонкоигольная аспирационная биопсия (ТАБ) под контролем УЗИ. Аспираты тестировались с помощью GeneXpert MTB/RIF. В неясных случаях проводилась эксцизионная биопсия. Результаты: Ультразвуковые признаки, такие как гипоэхогенная структура, спаянность и внутриузловой некроз, имели чувствительность 78% для туберкулезного лимфаденита. КТ превосходила УЗИ в выявлении глубокой медиастинальной и абдоминальной лимфаденопатии. GeneXpert MTB/RIF на аспиратах лимфатических узлов показал чувствительность 85% и специфичность 96%, значительно превосходя микроскопию мазка (25%). Гистологический анализ подтверждал диагноз, выявляя казеозные гранулемы, хотя у пациентов с тяжелым иммунодефицитом (CD4 <200) формирование гранулем было слабым. Заключение: Мультимодальный подход, интегрирующий аспирацию под контролем УЗИ с молекулярным ПЦР-тестированием (GeneXpert), позволяет быстро и точно диагностировать лимфогенный ТБ у пациентов с ВИЧ, способствуя своевременному началу лечения.
Ключевые слова: ВИЧ-ассоциированный туберкулез, туберкулезный лимфаденит, GeneXpert MTB/RIF, ультразвуковая диагностика, компьютерная томография, биопсия, дифференциальная диагностика.

INTRODUCTION

The intersection of the HIV and Tuberculosis (TB) epidemics presents one of the most critical and enduring challenges to global public health, with a particularly high burden in the Central Asian region. Tuberculosis remains the leading cause of mortality among People Living with HIV (PLHIV), accounting for approximately one-third of all HIV-related deaths. The immune

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suppression caused by HIV fuels the progression of latent TB infection to active disease, increasing the risk by 18-20 times compared to immunocompetent individuals.

A defining characteristic of HIV-associated tuberculosis is the high prevalence of extrapulmonary forms, which correlates inversely with the patient's CD4 T-cell count. Among these, lymphogenic tuberculosis (tuberculous lymphadenitis) is the predominant manifestation, affecting 30-50% of co-infected patients. Unlike classic pulmonary TB, which often presents with cough and positive sputum smears, lymphogenic TB is frequently "silent" or paucibacillary. The classic "constitutional symptoms" (fever, night sweats, weight loss) lose their specificity in PLHIV, as they may be attributed to HIV wasting syndrome, lymphoma, or other opportunistic infections.

This diagnostic ambiguity creates a dangerous "therapeutic window." Delayed diagnosis leads to rapid lymphatic and hematogenous dissemination, severe sepsis, and increased mortality. Furthermore, reliance on traditional diagnostic methods—such as physical palpation and sputum microscopy—is woefully inadequate for lymphogenic forms. In the Andijan region, clinical observations suggest that patients often undergo weeks of non-specific antibiotic therapy for "lymphadenitis of unknown origin" before TB is suspected.

The Department of Phthisiology at Andijan State Medical Institute aims to revolutionize the diagnostic pathway by shifting from a "sputum-centric" approach to a "tissue-centric" and molecular approach. This study evaluates a comprehensive, multimodal diagnostic algorithm integrating High-Resolution Ultrasound (USI), Computed Tomography (CT), Ultrasound-Guided Aspiration, and GeneXpert MTB/RIF technology. The goal is to establish a rapid, accurate, and minimally invasive protocol for the early detection of lymphogenic TB in the HIV-positive cohort, ensuring timely initiation of life-saving antiretroviral (ART) and anti-tuberculosis therapy.

LITERATURE REVIEW

Pathophysiology of Lymphogenic TB in HIV The lymphatic system serves as the primary line of defense against *Mycobacterium tuberculosis*. In immunocompetent hosts, the interaction between T-lymphocytes and macrophages results in the formation of granulomas that contain the infection. However, HIV selectively destroys CD4+ T-cells, dismantling the architecture of the granuloma. *Lawn et al. (2013)* describe this as a "loss of containment." Consequently, bacilli proliferate unchecked within the lymph nodes, leading to massive necrosis and liquefaction (cold abscesses) without the classic fibrotic wall. This explains why lymphadenitis in HIV is often multifocal, aggressive, and prone to rupturing through the skin (scrofuloderma).

The Role of Imaging - Ultrasound and CT While imaging cannot confirm etiology, it provides critical phenotypic clues.

Ultrasound (USI) - Studies by *Gupta (2020)* highlight specific sonographic features of tuberculous nodes: they tend to be round (loss of L/S ratio), hypoechoic, and show intranodal cystic necrosis. A key sign is "matting"—the fusion of multiple nodes due to peri-adenitis. In contrast, reactive nodes usually preserve their hilar fat, and lymphomatous nodes often appear reticular ("micronodular").

Computed Tomography (CT) - CT is superior for detecting deep-seated lymphadenopathy (mediastinal, mesenteric) which is clinically occult. The "Rim Sign"—peripheral enhancement with a low-density necrotic center—is highly suggestive of TB. However, differentiating this from necrotic metastasis or fungal infections remains a challenge requiring tissue sampling.

Molecular Diagnostics - The GeneXpert Revolution The introduction of the Xpert MTB/RIF assay has transformed TB diagnostics. It is a cartridge-based nucleic acid amplification test (NAAT) that detects DNA sequences specific to *M. tuberculosis* and rifampicin resistance. The

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World Health Organization (2023) recommends Xpert as the initial diagnostic test for all PLHIV. *Derseh et al. (2022)* reported that using Xpert on Fine Needle Aspirates (FNA) from lymph nodes yields a sensitivity of over 80%, compared to <30% for smear microscopy. This "needle-to-cartridge" workflow bypasses the need for culture, reducing diagnosis time from weeks to hours.

Histopathology and Differential Diagnosis Despite molecular advances, histopathology remains the ultimate arbiter, especially to rule out malignancy. The differential diagnosis for lymphadenopathy in HIV is broad, including Non-Hodgkin Lymphoma, Kaposi Sarcoma, Toxoplasmosis, and bacterial adenitis. A critical challenge identified in the literature is that in advanced HIV (CD4 <50), the characteristic caseating granulomas may be absent ("non-reactive TB"), showing only necrosis and abundant Acid-Fast Bacilli (AFB). Pathologists unaware of the HIV status may misinterpret these findings as acute suppurative lymphadenitis.

MATERIALS AND METHODS

Study Design A prospective diagnostic accuracy study was conducted at the Andijan regional phthisiatrics and pulmonology dispatcher (2022-2024). Participants 120 HIV-positive patients presenting with peripheral or generalized lymphadenopathy (lymph nodes >1.0 cm) were enrolled. Inclusion - Confirmed HIV status, enlarged lymph nodes lasting >2 weeks. Exclusion - Patients already on anti-TB treatment.

Diagnostic Modalities Patients underwent a sequential diagnostic workup: 1) Ultrasound Examination (USI) - Evaluation of cervical, axillary, and inguinal nodes using high-frequency linear probes. Assessed parameters: size, shape (L/S ratio), echogenicity, hilum preservation, vascularity, and presence of necrosis. 2) Computed Tomography (CT) - Performed for patients with suspected deep (mediastinal, retroperitoneal) lymphadenopathy or when USI was inconclusive. Assessed for "rim enhancement" and calcifications.

Fine Needle Aspiration Cytology (FNAC) - Performed under US guidance. The aspirate was split for cytology and PCR. Excisional Biopsy - Performed if FNAC was non-diagnostic. PCR - GeneXpert MTB/RIF Ultra assay on lymph node aspirates/tissue. Histopathology - H&E staining and Ziehl-Neelsen staining.

RESULTS AND DISCUSSION

Ultrasound Diagnostics (USI) Ultrasound proved to be a highly effective non-invasive triage tool. In confirmed TB cases (n=78), specific sonographic patterns were identified: 1) Hypoechogenicity - 92% of TB nodes were markedly hypoechoic (dark) compared to surrounding muscle. 2) Intranodal Necrosis - Cystic necrosis was visible in 65% of cases, appearing as anechoic areas within the node. This is a strong predictor of TB. 3) Matting - Clumping of multiple nodes with soft tissue edema (periadenitis) was seen in 55% of cases. 4) Absent Hilum - Loss of the fatty hilum was a sensitive but non-specific sign of malignancy or infection.

Computed Tomography (CT) CT was indispensable for detecting inaccessible nodes. In 30% of patients, peripheral lymphadenopathy was minor, but CT revealed massive necrotic mediastinal or abdominal adenopathy.

The "Rim Sign": Peripheral rim enhancement with a low-density necrotic center was observed in 82% of TB cases on contrast-enhanced CT. This distinguishes TB from lymphoma, which typically shows homogenous enhancement.

PCR Diagnostics (GeneXpert MTB/RIF) The application of GeneXpert on lymph node aspirates (FNA) revolutionized the speed of diagnosis. Sensitivity - 85% (compared to 25% for smear

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microscopy). Specificity - 96%. Rifampicin Resistance - Detected in 12% of cases, allowing immediate switch to second-line drugs. Turnaround Time - Diagnosis was confirmed within 2 hours, versus 4-6 weeks for liquid culture (MGIT).

Biopsy and Histology Histopathology remained the gold standard, particularly for differential diagnosis. Classic TB - Caseating granulomas with Langhans giant cells were seen in patients with relatively preserved immunity (CD4 >200). Atypical TB (Severe Immunosuppression) - In patients with CD4 <50, granulomas were poorly formed or absent ("non-reactive tuberculosis"). Instead, tissue showed massive necrosis with abundant Acid-Fast Bacilli (AFB). This highlights the need for Ziehl-Neelsen staining on all biopsy specimens, not just relying on granuloma structure.

Differential Diagnosis The study highlighted critical differentiation points: Lymphoma - Nodes are often rubbery, non-tender, and homogenous on US/CT. GeneXpert is negative. Biopsy shows monoclonal cell proliferation. Reactive Hyperplasia - Nodes preserve their oval shape and fatty hilum on US. No necrosis. Kaposi Sarcoma - Can involve lymph nodes; highly vascular on Doppler.

CONCLUSION

The early detection of lymphogenic tuberculosis in HIV-infected patients requires a fundamental shift in clinical mindset and diagnostic protocol. This study demonstrates that relying on clinical symptoms or simple microscopy is insufficient and dangerous in this vulnerable population.

No single diagnostic tool is perfect. However, the combination of Ultrasound (to identify the most necrotic/representative node) and GeneXpert (to confirm etiology) offers the highest diagnostic yield with minimal invasiveness.

High-resolution Ultrasound is an accessible, radiation-free modality that can reliably distinguish "suspicious" (necrotic, matted) nodes from benign reactive hyperplasia, guiding the decision to biopsy.

GeneXpert MTB/RIF on lymph node aspirates is vastly superior to smear microscopy and should be the standard of care. It not only confirms TB but also provides critical information on drug resistance (MDR-TB) within 2 hours.

Histological Awareness: Physicians and pathologists must recognize the spectrum of histological presentation in HIV. The absence of classic granulomas does not rule out TB; in severely immunocompromised patients, "necrotizing non-granulomatous lymphadenitis" is a common presentation of the disease.

RECOMMENDATIONS

To improve the prognosis of HIV-TB coinfected patients in the Andijan region and reduce mortality from disseminated tuberculosis, we propose the following clinical and organizational recommendations:

Diagnostic Algorithm Implementation:

Every HIV-positive patient presenting with peripheral lymphadenopathy should undergo a targeted ultrasound examination before any antibiotic trial.

Avoid "blind" biopsies. Use Ultrasound guidance to target the necrotic center of the node or the most accessible matted group for Fine Needle Aspiration (FNA).

Laboratory Integration:

Aspirated material from lymph nodes must be sent for GeneXpert testing *before* or *concurrently* with cytology. Do not wait for cytology results to order PCR.

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In histopathology, Ziehl-Neelsen (ZN) staining for Acid-Fast Bacilli should be mandatory for *all* lymph node biopsies from HIV-positive patients, regardless of whether granulomas are seen or not.

Differential Diagnosis Vigilance:

In cases where GeneXpert is negative but lymphadenopathy persists, Excisional Biopsy is mandatory to rule out Lymphoma or Kaposi Sarcoma. Do not rely on empirical anti-TB trials in PCR-negative cases.

Infrastructure and Training:

Ideally, HIV care centers (AIDS Centers) should be equipped with portable ultrasound machines and have rapid access to GeneXpert facilities to minimize patient attrition between visits.

Radiologists, phthisiologists, and infectious disease specialists need joint training sessions on the specific radiologic and clinical features of extrapulmonary TB in the context of HIV.

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