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MORPHOLOGICAL FEATURES OF LATE-DETECTED TUBERCULOSIS IN PATIENTS WITH ACQUIRED IMMUNODEFICIENCY

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Abstract: This article analyzes the morphological, immunological, and histopathological features of tuberculosis detected at a late stage in patients with acquired immunodeficiency. The research was conducted under the conditions of Uzbekistan, particularly in the Fergana region, and revealed that in cases of delayed diagnosis, granulomatous reactions are weakened, caseous necrosis predominates, and distinctive morphological differences are linked to immunohistochemical markers. The findings provide a significant scientific basis for improving early detection strategies for tuberculosis in immunodeficient individuals.

Keywords: tuberculosis, immunodeficiency, morphology, immunohistochemistry, granuloma, HIV.

INTRODUCTION

In modern epidemiological conditions, the coexistence of tuberculosis (TB) and HIV infection remains one of the most serious threats to global health systems. Worldwide, approximately 10 million new tuberculosis cases are identified annually, 8–10% of which are associated with HIV co-infection [7][9].

In immunodeficient patients, delayed detection of tuberculosis not only complicates diagnosis but also reduces treatment effectiveness and increases mortality.

According to statistics, individuals living with HIV have an 18–20 times higher risk of developing tuberculosis compared to immunocompetent individuals [7]. Moreover, latent or atypical forms of the disease occur in 35–50% of such patients, delaying clinical diagnosis [5][6]. In these cases, the absence of classical granulomatous reactions can cause the disease to manifest clinically and radiologically as latent. Epidemiological data show that delayed diagnosis rates reach 40–45% in Africa, Southeast Asia, and CIS countries [8][14].

Recent international analyses confirm that late-detected tuberculosis cases in HIV-positive individuals have reached up to 45% in Africa and Southeast Asia [5][6]. In the CIS region, particularly in Uzbekistan and Kazakhstan, the incidence of HIV-associated tuberculosis has been increasing by 6–8% annually [8][14]. These indicators underscore the urgent need to study the course of tuberculosis under immunodeficient conditions. Previous morphological studies [12][16] have highlighted that, instead of classical granulomas, delayed-diagnosis cases are dominated by diffuse inflammation, necrosis, and cellular destruction. Therefore, research in this area has become an essential issue not only in clinical practice but also in pathological anatomy.

In the CIS region, including Uzbekistan, Kazakhstan, Tajikistan, and Kyrgyzstan, an increase in late-detected tuberculosis forms has been observed. According to reports by the CIS Health Organization (2023–2024), HIV-associated TB cases in the region are increasing annually by an average of 12–15%, revealing gaps in early diagnostics [8,14].

In Uzbekistan, particularly in the Fergana Valley, data from the 2024 report of the Republican Phthisiology Center show that HIV-associated, late-diagnosed tuberculosis cases accounted for 14.7% of total morbidity, reaching up to 16.2% in Andijan and Namangan regions [8]. Similarly, morphological observations conducted in Kazakhstan (Almaty and Shymkent regions) in 2024 revealed that 20% of delayed TB cases occurred under immunosuppressive conditions [14]. In

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Tajikistan, TB-related mortality among HIV-positive patients was 9.5%.

These findings indicate the need for detailed immunological, histopathological, and molecular research since regional climatic, epidemiological, and social factors directly influence disease progression. In the Fergana Valley, delayed-diagnosis cases are particularly common among socially vulnerable groups (HIV-positive individuals, intravenous drug users, long-term prisoners), making the improvement of morphological diagnostic methods a critical issue.

This study aims to fill this scientific gap by analyzing the diagnostic significance of morphological and immunohistochemical indicators for improving early detection of tuberculosis in immunocompromised patients. The work also explores immunopathological mechanisms of tuberculosis, evaluating both clinical manifestations and cellular-level alterations. In particular, cytokine imbalance (IL-2, IL-6, IL-10), macrophage dysfunction, and disturbances in granuloma formation in HIV-positive patients are examined. Statistical data show that in 35–40% of delayed-diagnosis cases, uncertain radiological features necessitated morphological confirmation.

Furthermore, with the rising incidence of pharmacoresistant forms in Central Asia, morphological analysis is gaining even greater relevance. This article proposes a new diagnostic algorithm integrating clinical, laboratory, and morphological approaches.

The main purpose of the study is to determine the morphological characteristics of tuberculosis detected late in patients with acquired immunodeficiency, to describe its pathogenesis based on immunohistochemical markers, and to develop differential criteria for early diagnosis.

Research objectives:

1. Classify HIV-associated tuberculosis patients according to immune status.
2. Evaluate granuloma formation and necrotic processes through histological analysis.
3. Identify pathological stages using immunohistochemical markers (CD68, TNF-α, IL-10, anti-MTB).
4. Compare morphological findings with clinical indicators (CD4/CD8).
5. Propose a diagnostic algorithm for early detection of late-diagnosed tuberculosis.

MATERIALS AND METHODS

The study involved 90 HIV-associated tuberculosis patients treated at Fergana regional phthisiology and infectious disease hospitals. Based on clinical, immunological, and laboratory parameters, patients were divided into three groups:

- CD4 > 350/μL (mild immunodeficiency, n=28),
- CD4 = 200–350/μL (moderate immunodeficiency, n=32),
- CD4 < 200/μL (severe immunosuppression, n=30).

Biopsies or autopsies were used to obtain lung, lymph node, and occasionally liver tissues. At least three sections per sample were prepared for microscopic examination.

Tissues were fixed in 10% neutral formalin and embedded in paraffin. Hematoxylin–eosin (H&E) staining was used for general morphology. Granuloma formation, epithelioid cell count, Langhans giant cells, necrosis depth, and fibrosis extent were each scored from 0–3. Ziehl–Neelsen staining was used to detect acid-fast bacilli (AFB), and colony counts were recorded.

Immunohistochemical (IHC) analysis was conducted using CD68, TNF-α, IL-10, IFN-γ, and anti-MTB markers. Antigen retrieval (citrate buffer, pH 6.0, 15 min) and DAB chromogen were applied. Reaction intensity was graded from "+" to "+++" and correlated with immune status (CD4 count). Macrophages and lymphocytes were counted across 100 fields, and an IHC index ($I = \Sigma(+x1)+(++x2)+(+++x3)$) was calculated.

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Electron microscopy (JEOL JEM-2100) was used to examine alveolar macrophages, lymphocyte nuclei, mitochondria, and phagolysosomal structures. Morphometric parameters—mitochondrial diameter, nucleus-to-membrane ratio, and lysosomal vacuole count—were measured. Ultrastructurally, mitochondrial swelling, endoplasmic reticulum dilation, and nuclear chromatin condensation were observed.

Statistical analysis was performed using SPSS v26 and GraphPad Prism v9.0. The Student's t-test was used for parametric data, Mann–Whitney for nonparametric data. Pearson and Spearman correlations were assessed at $p < 0.05$ significance.

RESULTS AND DISCUSSION

Findings revealed that tuberculosis in immunodeficient patients deviates from the classical granulomatous form, presenting atypical morphology. In CD4 < 200/μL patients, incomplete granuloma formation occurred in 62% of cases, lacking epithelioid and Langhans giant cells. Instead, diffuse inflammation with predominant caseous necrosis appeared in 71% of cases, indicating failure to generate an adequate granulomatous response.

Immunohistochemically, CD68-positive macrophage infiltration was pronounced, but phagocytic activity was reduced. Moderate TNF-α expression (+/++) indicated persistent inflammation, while high IL-10 expression (++/+++) confirmed enhanced immunosuppression—demonstrating impaired defense mechanisms.

Electron microscopy showed mitochondrial destruction in alveolar macrophages (48%) and phagolysosomal dysfunction (43%). Such ultrastructural changes, particularly in patients with CD4 < 200/μL, confirmed deep cellular-level alterations in TB pathogenesis. Statistical analysis ($p < 0.05$) demonstrated significant correlations between morphological and immunological indices.

Compared with international studies, these findings were consistent with Huang S. [1] and Kacprzak A. [2], confirming that diminished granuloma formation is strongly associated with diagnostic delay. However, while Diedrich C. [3] reported complete granuloma loss, our study showed partial preservation under moderate immunodeficiency—reflecting regional immunological peculiarities.

Overall, the study emphasizes the need for new morphological diagnostic approaches in immunocompromised TB patients. Even in the absence of classical granulomas, diffuse necrosis and immunohistochemical markers can guide diagnosis. Hence, implementing biopsy, IHC, and electron microscopy in clinical practice is crucial. Additionally, monitoring immunoregulatory cytokines (IL-2, IL-6, IL-10) can serve as an important prognostic tool [18].

In some patients, low TNF-α levels enhanced necrotic destruction, whereas persistent CD68 expression indicated macrophage functional exhaustion [15]. Studies from China and India have similarly shown that Mycobacterium tuberculosis can be detected through diffuse necrosis even when granulomatous structures are absent [24]. In patients with low CD4 counts, elevated IL-6 and IL-10 levels reflected restricted inflammation yet poor infection control. Suppressed TNF-α disrupted granuloma stability and reduced macrophage bactericidal activity. Morphometric analyses confirmed reduced granuloma area and increased necrotic mass.

Importantly, in immunodeficient patients, these morphological processes often mimic diffuse pneumonia, leading to diagnostic errors. Therefore, beyond radiology, biopsy and IHC must be integrated into diagnostic protocols—forming the basis for new clinical guidelines.

CONCLUSION AND RECOMMENDATION

This study scientifically confirmed that in patients with acquired immunodeficiency, the course of tuberculosis differs markedly from its classical form. In late-diagnosed cases, granulomatous

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inflammation is weakened, and caseous necrosis predominates. Morphometric analysis revealed an inverse correlation between CD4 count and granuloma size, necrotic area, and epithelioid cell density.

In moderate immunodeficiency, granuloma area averaged 0.35 ± 0.02 mm², whereas in severe immunosuppression, it decreased to 0.12 ± 0.01 mm² ($p < 0.05$). A significant correlation ($r = 0.67$) was found between IL-10, TNF-α, and CD68 expression levels. Morphological and immunohistochemical findings confirmed that reduced CD4 counts lead to impaired granuloma formation, decreased macrophage phagocytic activity, and enhanced IL-10-mediated immunosuppression.

Electron microscopy demonstrated macrophage destruction, mitochondrial damage, phagolysosomal dysfunction, and endoplasmic reticulum swelling—indicating deep cellular impairment in TB pathogenesis. Alveolar macrophages exhibited reduced lysosomal enzyme activity and increased apoptotic tendency. These findings elucidate the morphological manifestation of immune imbalance in HIV-associated TB.

Scientific and practical recommendations:

1. Morphological diagnosis of HIV-associated tuberculosis should not rely solely on granuloma presence but also assess necrotic and immunohistochemical markers.
2. Early differential diagnosis using CD68, TNF-α, and IL-10 markers can reduce delayed detection cases.
3. Develop and implement a special diagnostic algorithm for late-diagnosed cases in Fergana and across Uzbekistan.
4. Include IHC methods in routine HIV/TB screening programs alongside PCR and GeneXpert.
5. Introduce educational modules on immunomorphological TB forms in medical universities and clinical centers.

Thus, this study provides a comprehensive morphological, immunological, and cellular analysis of tuberculosis under immunodeficient conditions in Uzbekistan and contributes to improving diagnostic and therapeutic approaches.

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