U.D.C.: 616.98:578.828:HIV616.24-002]-078:57.083.3
DOI: https://doi.org/10.52692/1857-0011.2025.3-83.03

THE INFLUENCE OF HIV INFECTION ON THE PROCESSES OF LUNG TISSUE REMODELING IN TUBERCULOSIS PATIENTS DURING ANTI-TB TREATMENT

Olga SHEVCHENKO[1], doctor of medical sciences, univer. professor,
Liliia TODORIKO[2], doctor of medical sciences, univer. professor,
Helen TUDOR[3], MD, PhD, member corr. of the AMSM
Iryna OVCHARENKO[4], MD, PhD, univer. teacher,
Olga POHORIELOVA[5], PhD, doctor
Sergiy OVCHARENKO[1], PhD, univer. teacher,

[1]Kharkiv National Medical University, Ukraine
[2]Bukovynian State Medical University, Ukraine
[3]PMSI Institute of Pneumonology "Chiril Draganiuc", Chisinau, Republic of Moldova
[4]Balti Medical College, Republic of Moldova
[5]MNE of KRC "Regional Clinical Psychiatric Hospital No. 3", Kharkiv, Ukraine
e-mail: *os.shevchenko@knmu.edu.ua*

Summary.
The adaptive immune response to tuberculosis develops approximately six weeks after infection. In HIV, this process is disrupted due to delayed activation of CD4 lymphocytes. Immune cells in combination with mycobacteria stimulate the synthesis of matrix metalloproteinase-9 (MMP-9), which breaks down collagen. Its breakdown product (hydroxyproline) is a biomarker of lung tissue destruction. The ratio of MMP-9 to tissue inhibitor of metalloproteinases-1 (TIMP-1) (MMP-9/TIMP-1) reflects the balance between degradation and repair of lung tissue. In addition, aldosterone plays an important role, as it can activate monocytes, enhance inflammation, disrupt fibrinolysis, and stimulate collagen synthesis by fibroblasts. Its elevated level is associated with the development of pulmonary fibrosis. In patients with MDR-TB without HIV infection, the processes of pulmonary tissue remodeling were more typical: the balance between MMP-9, TIMP-1, and hydroxyproline was maintained, which contributed to the development of fibrosis and limitation of inflammation. In patients with TB/HIV coinfection, there was a marked imbalance in fibrosis factors: increased levels of MMP-9 and hydroxyproline with insufficient activation of TIMP-1, which led to a more generalized process and worse clinical outcomes. Aldosterone levels decreased during treatment in both groups, but this decrease was less pronounced in TB/HIV patients, confirming abnormalities in the fibrosis system in this group of patients.

Key words: tuberculosis, HIV infection, matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1, oxyproline, aldosterone.

Rezumat. Influența infecției cu HIV asupra proceselor de remodelare a țesutului pulmonar la pacienții cu tuberculoză în timpul tratamentului antituberculos.
Răspunsul imun adaptiv la tuberculoză se dezvoltă la aproximativ șase săptămâni după infecție. În cazul HIV, acest proces este perturbat din cauza activării întârziate a limfocitelor CD4. Celulele imune, în combinație cu micobacteriile, stimulează sinteza metaloproteinazei matriceale-9 (MMP-9), care descompune colagenul. Produsul său de descompunere (hidroxiprolina) este un biomarker al distrugerii țesutului pulmonar. Raportul dintre MMP-9 și inhibitorul tisular al metaloproteinazelor-1 (TIMP-1) (MMP-9/TIMP-1) reflectă echilibrul dintre degradarea și repararea țesutului pulmonar. În plus, aldosteronul joacă un rol important, deoarece poate activa monocitele, poate accentua inflamația, poate perturba fibrinoliza și poate stimula sinteza colagenului de către fibroblaste. Nivelul său crescut este asociat cu dezvoltarea fibrozei pulmonare. La pacienții cu tuberculoză multidrogrezistentă (MDR-TB) fără infecție cu HIV, procesele de remodelare a țesutului pulmonar au fost mai tipice: echilibrul dintre MMP-9, TIMP-1 și hidroxiprolină a fost menținut, ceea ce a contribuit la dezvoltarea fibrozei și limitarea inflamației. La pacienții cu coinfecție TB/HIV, a existat un dezechilibru marcat al factorilor de fibroză: niveluri crescute de MMP-9 și hidroxiprolină cu activare insuficientă a TIMP-1, ceea ce a dus la un proces mai generalizat și la rezultate clinice mai slabe. Nivelurile de aldosteron au scăzut în timpul tratamentului în ambele grupuri, dar această scădere a fost mai puțin pronunțată la pacienții cu TB/HIV, confirmând anomalii ale sistemului de fibroză la acest grup de pacienți.

Cuvinte cheie: tuberculoză, infecție cu HIV, metaloproteinază matriceală-9, inhibitor tisular al metaloproteinazei-1, oxiprolină, aldosteron.

Introduction.

Tuberculosis (TB) and HIV infection are among the most significant medical and social problems worldwide and in Ukraine in particular [1]. Tuberculosis incidence has risen again in recent years after a long-term downward trend [1], and the incidence of HIV infection continues to grow. The military conflict in Ukraine is exacerbating the epidemic situation both in terms of each disease individually and in terms of their combination.

People living with HIV (PLHIV) have, on average, a 19-fold higher risk of developing tuberculosis compared with HIV-negative individuals, as HIV substantially modifies the clinical course of tuberculosis, while Mycobacterium tuberculosis (MTB) influences the immune response in HIV-infected patients. [2]. Characteristics of the immune response during coinfection include a lower incidence of destructive forms of TB, changes in bacterioscopy results, and differences in blood counts. A decrease in CD4 lymphocyte count suppresses an adequate immune response to MTB, accelerating infection progression. [3]. Even with a normal CD4 count, the risk of TB in PLHIV remains significantly higher [4].

The adaptive immune response in TB develops approximately six weeks after infection, accompanied by a positive tuberculin skin test. In HIV, this process is disrupted due to delayed CD4 cell activation. Macrophages also play a key role, with their functional activity altered by MBT [5].

Immune cells, in combination with mycobacteria, stimulate the synthesis of matrix metalloproteinase-9 (MMP-9), which breaks down collagen. Its breakdown product (hydroxyproline) is a biomarker of lung tissue destruction. TIMP-1, a tissue inhibitor of metalloproteinases, plays a key role in regulating protease activity during pathological processes. [6] Predominance of TIMP-1 leads to capillary degradation within tissues, whereas elevated levels of MMP-9 result in extracellular matrix destruction.

The ratio (MMP-9/TIMP-1) of MMP-9 and tissue inhibitor of metalloproteinases-1 (TIMP-1) reflects the balance between lung tissue degradation and restoration. Under physiological conditions, this ratio approaches unity. [6; 7].

Along with this, aldosterone plays an important role, being able to activate monocytes, increase inflammation, disrupt fibrinolysis and stimulate collagen synthesis by fibroblasts. [8; 9]. Its elevated levels are associated with the development of pulmonary fibrosis. [10; 11].

The purpose of the study was to compare the dynamics of MMP-9, TIMP-1, total oxyproline and aldosterone in patients with multidrug-resistant tuberculosis with HIV and patients with multidrug resistant tuberculosis without HIV.

Materials and methods.

The study included 56 patients with new cases of MTB-positive multidrug-resistant tuberculosis (MDR-TB). The patients were divided into 2 groups: Group 1 (n=16) included patients with TB/HIV coinfection; Group 2 (n=40) included HIV-negative patients.

In patients of Group 1 HIV was diagnosed during TB examination. Antiretroviral treatment was prescribed in 2-8 weeks after start of antimycobacterial treatment according to the order of the Ministry of Health of Ukraine in force at the time of the study. TB treatment was carried out in accordance with current regulatory documents.

The groups were matched for age (39 and 37 years, respectively) and gender (male to female ratio 1:1). Examinations were performed before treatment and after 2 months and included clinical, laboratory, and instrumental methods, as well as determination of fibrosis biomarkers (total hydroxyproline, MMP-9, TIMP-1, and aldosterone).

Hydroxyproline levels were determined using the Sharaev PN method with CPK-2 photometry. MMP-9 and TIMP-1 levels were determined using an enzyme immunoassay method, and aldosterone was measured using standard ELISA test systems. Statistical analysis was performed using the nonparametric Mann-Whitney and Wilcoxon tests, as well as Spearman's correlation analysis.

Results.

At the start of treatment, MTB was detected by culture in 100% of patients in both groups. Sputum microscopy was positive in 50% of patients with HIV/TB and in 90% of patients without HIV.

After two months of treatment, the number of patients with bacterial excretion in Group I decreased: by 2-fold by microscopy and by 4-fold by culture. In Group II, the number of positive results decreased almost twofold (42% by microscopy and 47% by culture).

Chest X-ray showed destructive lung changes in 50% of patients in Group I and 95% of patients in Group II. After four months, positive dynamics (resorption and consolidation) were recorded in 25% of patients with TB/HIV and 50% of patients without HIV.

Table 1 shows that in Group 1, the MMP-9 level was 11% lower, but after 2 months it significantly increased by 18.4%. No changes were observed in Group 2. The TIMP-1 level at the beginning of treatment was 17.3% higher in patients with TB/

Table 1.

Levels of fibrosis markers in patients at the start of antimycobacterial treatment and in 2 months (Me)

		MMP-9 (ng/ml)	TIMP-1 (ng/ml)	MMP-9/ TIMP-1	Total oxyproline (mg/l)	Aldosterone (pg/ml)
Group	**Test**	**Me**	**Me**	**Me**	**Me**	**Me**
1	Treatment onset	326.5	154.6	2.11	3.95	92
	In 2 months	386.4	174	2.22	5.2	54.2
2	Treatment onset	361.4	127.8	2.83	3.33	91.4
	In 2 months	363.2	160.2	2.27	3.15	64.9

HIV, and increased in 2 months in both groups (by 12.5% and 25%, respectively). The MMP-9/TIMP-1 ratio was initially higher in HIV-negative patients (by 25.5%). During treatment, it decreased by 19.8% in Group 2. In Group I, it increased by 5.2%.

Total oxyproline was higher in Group 1 at the beginning of treatment and increased by 31.6% during the observation period. In Group 2, it remained virtually unchanged (a decrease of 5%).

The aldosterone level at the start of treatment did not differ significantly, but decreased over 2 months by 29% in Group 2 and by 40% in Group 1.

Discussion.

Normally, MMP-9 activity is regulated by TIMP-1, and lung cells do not express it in the absence of pathology. [12]. During inflammation, the synthesis of MMP-9 increases [13]. In TB patients, the enzyme level can be 3 times higher than normal.

In our study, HIV-negative patients maintained a relative balance due to elevated TIMP-1, as evidenced by the increasing correlation between these parameters. A decrease in the MMP-9/TIMP-1 ratio was accompanied by positive clinical dynamics (sputum conversion, decreased destruction of lung tissue).

Patients with TB/HIV showed unstable dynamics: an increase in MMP-9 with an insufficient increase in TIMP-1, high hydroxyproline levels, and a delayed decline in aldosterone. This reflected an imbalance in proteolysis and collagen synthesis, which was accompanied by a more severe clinical course, less positive X-ray dynamics, and signs of generalization.

Conclusions.

In MDR-TB patients without HIV infection, lung tissue remodeling processes were more typical: a balance between MMP-9, TIMP-1, and hydroxyproline was maintained, promoting fibrosis and limiting inflammation. Patients with TB/HIV co-infection demonstrated a pronounced imbalance of fibrosis factors: increased MMP-9 and hydroxyproline with insufficient TIMP-1 activation, leading to a more generalized process and worse clinical outcomes. Aldosterone levels decreased during treatment in both groups, but the decrease was less pronounced in TB/HIV patients, confirming disruptions in the fibrosis-forming system in this group of patients.

References.

1. Global tuberculosis report 2024. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.
2. HIV-Associated Tuberculosis. Available online: https://www.who.int/tb/areas-of-work/tb-hiv/tbhiv_factsheet.pdf
3. Sakai S, Mayer-Barber KD, Barber DL. *Defining Features of Protective CD4 T cell responses to Mycobacterium tuberculosis*. Current Opinion in Immunology. 2015;0:137-142.
4. Tornheim JA, Dooley KE. *Tuberculosis Associated with HIV Infection.* Microbiology Spectrum. 2017;5(1).
5. Auld SC, Staitieh BS. *HIV and the tuberculosis "set point": how HIV impairs alveolar macrophage responses to tuberculosis and sets the stage for progressive disease.* Retrovirology. 2020;32(17).
6. Kubler A, Luna B, Larsson C, Ammerman NC, Andrade BB, Orandle M, Bishai WR. *Mycobacterium tuberculosis dysregulates MMP/TIMP balance to drive rapid cavitation and unrestrained bacterial proliferation*. Journal of Pathology. 2015;235(3):431-444.
7. Shevchenko O.S, Todoriko L.D, Ovcharenko I.A, Pohorielova O.O, Shvets O.M. *Analysis of changes in matrix metalloproteinases-9 and tissue inhibitors-1 levels in newly diagnosed pulmonary tb with different profile of drug-resistance*. Tuberculosis, Lung Diseases, HIV Infection. 2022;3:5-10.
8. Shieh FK, Kotlyar E, Sam F. *Aldosterone and cardiovascular remodelling: focus on myocardial failure.* Journal of the Renin Angiotensin Aldosterone System. 2004;5(1):3-13.
9. Shevchenko OS, Todoriko LD, Ovcharenko IA, Radzishevska YB, Shvets OM, Ovcharenko SS, Semianiv IO, Vivsyannuk VV. *Dynamics of aldosterone, connective tissue reorganization and glucose level as markers for tuberculosis treatment*

effectiveness. Archives of the Balkan Medical Union. 2019;54(2):274–280.
10. Hung C-S, Chou C-H, Liao C-W, Lan Y-T, Wu X-M, Chang Y-Y, et al. *TAIPAI Study Group. Aldosterone Induces Tissue Inhibitor of Metalloproteinases-1 Expression and Further Contributes to Collagen Accumulation: From Clinical to Bench Studies.* Hypertension. 2016;67(6):1309-1320.
11. Shevchenko OS, Ovcharenko IA, Todoriko LD. *Pathophysiological mechanisms destruction of the lung connective tissue in tuberculosis*. Infusion & Chamotherapy. 2019;2(2):14-20.
12. Amalinei C, Caruntu ID, Giusca SE, Bălan RA. *Matrix metalloproteinases involvement in pathologic conditions.* Romanian Journal of Morphology and Embryology. 2010;51(2):215-228.
13. Sabir N, Hussain T, Mangi MH, Zhao D, Zhou X. *Matrix metalloproteinases: Expression, regulation and role in the immunopathology of tuberculosis*. Cell Proliferation. 2019;52(4):e12649.