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Parameters of the MMP / TIMP system in assessing the clinical course of pulmonary tuberculoma

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ABSTRACT

Aim. To study the parameters of the matrix metalloproteinase (MMP) / tissue inhibitors of metalloproteinase (TIMP) system in assessing the clinical course of pulmonary tuberculoma.

Materials and methods. We examined 87 patients (55 men and 32 women), average age 33 [28; 43] years, with a morphologically and bacteriologically confirmed diagnosis of tuberculoma, who received treatment at St. Petersburg Research Institute of Phthisiopulmonology. In all patients, computed tomography of the chest, fiberoptic bronchoscopy, and lung function tests were performed. In the blood serum, concentrations of MMP-1, -8, -9, and their tissue inhibitor TIMP-1 were determined using ELISA (R&D Systems, USA), and the activity of α_2-macroglobulin (MG) was determined by the enzyme assays. For statistical data processing, Statistica 10.0 and R were used.

Results. In the study group, single and multiple tuberculomas were revealed in 37 and 63% of cases, respectively, necrotic areas – in 50% of patients, external respiration disorders – in 48% of cases, and catarrhal bronchitis (CB) – in 77% of cases. Tobacco smokers (TS) were identified in 69% of cases. Significant differences between MMP concentrations allowed us to distinguish four patterns from the characteristics adopted for the clinical and radiological assessment of disease intensity. It was shown that an increase in the levels of MMP-1 and MMP-9 can be a predictor of tuberculoma progression caused by a diffuse process with necrotic areas and bronchogenic dissemination (pattern 1, 2). Changes in the levels of MMP-8, TIMP-1 or MG (pattern 3, 4) were associated with permanent exposure to a non-specific component of inflammation (TS or CB).

Conclusion. Changes in the MMP / TIMP system parameters can be used as objective laboratory protein biomarkers to assess the clinical course of pulmonary tuberculoma.

Keywords: extracellular matrix, matrix metalloproteinases, tissue inhibitors of metalloproteinases, pulmonary tuberculoma

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Показатели системы «матриксные металлопротеиназы и ингибиторы периферической крови» в оценке клинического течения туберкулемы легких

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РЕЗЮМЕ

Цель. Изучить возможность использования показателей системы «матриксные металлопротеиназы (ММП) / ингибиторы периферической крови» в оценке клинического течения туберкулемы легкого.

Материалы и методы. Обследованы 87 больных (55 мужчин и 32 женщины), средний возраст 33 [28; 43] года, с бактериологически и морфологически верифицированным диагнозом «туберкулема», находившихся на лечении в ФГБУ «СПб НИИФ» Минздрава России. Всем пациентам выполнены компьютерная томография органов грудной клетки, фибробронхоскопия и оценка функции внешнего дыхания (ФВД). В сыворотке крови определяли концентрации ММП-1, -8, -9 и их тканевого ингибитора ТИМП-1 методом ELISA (R&D Systems, США), а также активность α2-макроглобулина (МГ) энзиматическим методом по торможению гидролиза N-бензоил-L-аргининэтилового эфира. Применяли Statistica 10.0 и R.

Результаты. В исследуемой группе единичные и множественные туберкулемы определены в 37 и 63% случаев соответственно, наличие распада – в 50%, нарушения ФВД – в 48% и неспецифические поражения трахеобронхиального дерева в виде катарального эндобронхита (КЭБ) – в 77% случаев. Табакокурильщики (ТК) выявлены в 69% случаев. Выделено четыре комбинации (паттерна) из характеристик, принятых для клинико-рентгенологической оценки активности специфического процесса, соответствующие различной степени повышения концентраций ММП в периферической крови. Показано, что повышение уровня ММП-1 и ММП-9 может являться предиктором прогрессирования туберкулемы, обусловленного распространенным процессом с наличием распада и бронхогенной диссеминации (паттерны № 1, 2). Изменения уровня ММП-8, ТИМП-1 или МГ отражают значимость вклада перманентного воздействия неспецифического компонента воспаления (ТК или КЭБ) в оценку тяжести специфического процесса и не исключают возможности его прогрессирования (паттерны № 3, 4).

Заключение. Изменения показателей системы «ММП / ингибиторы периферической крови» могут быть использованы в качестве объективных лабораторных белковых биомаркеров для оценки клинического течения специфического процесса при туберкулеме легких.

Ключевые слова: внеклеточный матрикс, матриксные металлопротеиназы, ингибиторы протеиназ, туберкулема легких

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено локальным этическим комитетом СПб НИИФ (протокол № 9 от 15.09.2016).

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INTRODUCTION

Pulmonary tuberculoma is a clinical form of tuberculosis that is presented by encapsulated caseous foci of more than 1.0 cm in diameter. These foci are different in genesis and are radiologically characterized by rounded shadows. Tuberculoma mainly originates from infiltrative and focal pulmonary tuberculosis [1]. In addition, tuberculoma can be imitated by a caseoma in cavernous tuberculosis. The proportion of tuberculoma in the tuberculosis prevalence in the Russian Federation is about 10%.

Clinical variants of the disease course reflect morphological differences in the development of specific inflammation. In case of a remitting course, tuberculoma results from resolution of an extensive pneumonic inflammatory infiltrate during its fading and demarcation. Caseous necrosis in this case has a homogenous nature, sometimes with foci of calcification (homogeneous tuberculomas). In case of a progressive course, on the contrary, tuberculoma is represented by a caseous pneumonic process growing from the center to the periphery, without grossly visible encapsulation and often without pronounced clinical manifestations (lamellar pattern of tuberculoma) [2, 3].

The assessment of the direction of specific inflammation in tuberculoma remains clinically relevant, as limited tuberculosis inflammation typically lacks signs of intoxication and bacterial excretion. The formed fibrous capsule prevents penetration of chemotherapy drugs into the focus of inflammation. Radiological signs of inflammation intensity in the presence of a fibrous capsule are limited and require a dynamic assessment of the size of tuberculoma for 2–3 months [4].

The potential danger of tuberculoma without bacterial excretion is determined by the probability of its progression due to possible drug resistance of the pathogen and the risk of treatment interruption by the patient due to subjective self-assessment of the condition. A morphological examination of the surgical material is the most objective method for predicting the direction of tuberculosis progression. At the same time, invasive methods for obtaining biological material have their limitations and contraindications, therefore, the search for protein biomarkers will contribute to expanding the arsenal of methods for objective assessment of the clinical course of the pathology [5].

Different phases of the clinical course of tuberculoma are based on changes in the lung parenchyma mediated by disturbances in the extracellular matrix (ECM) metabolism, characterized by an increase in the volume of the lesion, necrotic areas, thinning of the tuberculoma capsule, or its fibrotic transformation [5]. Matrix metalloproteinases (MMPs) belong to the family of extracellular zinc-dependent proteolytic enzymes involved in the ECM metabolism. They are end effectors of the innate immune response. The pathophysiological role of MMPs is associated with their involvement in the development and maintenance of inflammation and modeling of the effects of cytokines, growth factors, and hormones. This allows to consider MMPs not only as markers of tissue destruction and remodeling but also, possibly, as contributors to the inflammation intensity. According to the substrate specificity, various families of MMPs are distinguished: collagenases, gelatinases, stromelysins, etc. [6].

Infection of cells with *M. tuberculosis* leads to an increase in the expression of pro-MMPs, causing an imbalance between activated MMPs and their

inhibitors, contributing to the destruction of lung tissue and dissemination [7]. The imbalance in the MMP / tissue inhibitors of metalloproteinase (TIMP) system underlies structural changes in the lung parenchyma, determining external respiration disorders in various lung diseases, including tuberculosis [8, 9].

An important condition for obtaining significant prognostic data is an adequate choice of methods for statistical processing of the material. The use of symptom analysis is effective when it is necessary to evaluate a dataset that is informative only when considered as a whole [10]. An advantage of this method is the ability to form groups that differ in a combination of characteristics that are not revealed when assessed in isolation.

The aim of the study was to investigate the parameters of the MMP / TIMP system in assessing the clinical course of pulmonary tuberculoma.

MATERIALS AND METHODS

We examined 87 patients (55 men and 32 women), average age 33 [28; 43] years, with a morphologically and bacteriologically confirmed diagnosis of tuberculoma, who received treatment at St. Petersburg Research Institute of Phthisiopulmonology from 2017 to 2021. Exclusion criteria were: diabetes, pregnancy, and chronic obstructive pulmonary disease. The control group consisted of 20 apparently healthy age- and sex-matched individuals. In 95% of the cases, tuberculoma formed due to the involution of infiltrative pulmonary tuberculosis against the background of long-term chemotherapy for up to 1 year. In case of bacterial excretion before treatment initiation, in 90% of cases, strains with multi-drug resistance of the pathogen to anti-tuberculosis drugs were detected.

The enzyme-linked immunosorbent assay (ELISA) was used to measure the concentrations of MMPs in the blood serum: collagenases MMP-1 and MMP-8; gelatinase MMP-9; and their tissue inhibitor TIMP-1 using the ELISA reagent kit (R&D Systems, USA) according to the manufacturer's instructions. The activity of α_2-macroglobulin (MG) was assessed by the enzyme assays based on inhibition of alpha-N-benzoyl-L-arginine ethyl ester hydrolysis (ICN, Biomedicals Inc., USA).

In all patients, computed tomography (CT) of the chest was performed on the SOMATOM Sensation 64-slice CT scanner with the assessment of structural changes in the lung parenchyma (Nodule Analysis and Lung Volume Analysis software package (LUNA16) and Lung Volume Analysis (Canon Medical Informatics, Inc., USA)) [11]. Lung function tests (spirometry, body plethysmography) were performed using the MasterScreen PFT diagnostic system (VIASYS Healthcare, Germany) in accordance with the criteria established by the American Thoracic Society and European Respiratory Society (ATS / ERS) [12]. Fiberoptic bronchoscopy was performed using the BF-B2 flexible fiberoptic bronchoscope (Olympus, Japan).

For statistical data analysis, the Statistica 10.0. (StatSoft Inc., USA) and R (free software environment) software packages were used. The logarithmic scale (Log) was used for a number of metric variables (parameters of the MMP / TIMP system) to reduce the asymmetry of distribution. Data were presented as the median (*Me* or *MeLog*) and the interquartile range (Q_1; Q_3). We used the Fisher's exact test, the Mann – Whitney *U*-test, and the Spearman's rank correlation coefficient (r). The symptomatic analysis revealed the most significant patterns for the parameters of the MMP / TIMP system; they were represented as logical functions of categorical variables [10]. In this case, the pattern was considered as a combination of characteristics from radiological, functional, and endoscopic research methods, represented as a certain logical function described by the polynomial over the finite field of characteristic 2. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at St. Petersburg Research Institute of Phthisiopulmonology (Protocol No. 9 of 15.09.2016).

RESULTS AND DISCUSSION

The study group of patients with tuberculoma was not homogeneous according to their radiological and functional characteristics. In half of the cases, necrotic areas were identified, in 54 (63%) of patients, X-ray revealed multiple necrotic foci. The median of the total volume of the foci was 5,700 mm^3 [2,920; 13,600], and the median of the total volume of necrotic areas was 192 mm^3 [0; 590]. The main parameters characterizing lung capacity were within acceptable ranges, although disturbances in airway patency were detected in every second patient (Table 1).

Among external respiration disorders, obstructive lung disease prevailed (60%). Restrictive lung disease was detected in isolated cases (7.1%), and no mixed patterns were found.

Non-specific changes in the bronchial mucosa with clinical manifestations of diffuse catarrhal bronchitis (CB) and a history of smoking were found in more than half of the patients. The median smoking index was 15 pack years [6.30; 22.50], with a smoking history of over 10 years in 87% of cases.

Table 1

Lung function parameters in patients with tuberculoma

Parameter	*Me* [Q_1; Q_3], *p*	Normal value
FVC, % from the predicted value	108.85 [95.80;121], >0.05	80–120
FEV_1, % from the predicted value	99.75 [93.0;100.2], >0.05	80–120
Gaensler index, %	78.6 [71.4;84], >0.05	>70
MMEF, % from the predicted value	77.0 [56.0;94.0], >0.05	>60

Note. FVC – forced vital capacity; FEV_1 – forced expiratory volume in one second, Gaensler index = FEV_1 / FVC (modified Tiffeneau index), MMEF – mean maximal expiratory flow between 25 and 75% of FVC; *p* – a statistical significance threshold compared to healthy individuals (Mann – Whitney *U*-test).

The intensity of the inflammation was characterised by a moderate increase in the levels of collagenases (MMP-1 and MMP-8) and a significant increase in gelatinase (MMP-9) against the background of decreased MG activity and the absence of significant changes in the TIMP-1 level in the peripheral blood (Table 2).

The binary analysis did not reveal any significant differences in metric variables (parameters of the MMP / TIMP system) for any of the selected categorical variables (Table 3).

The symptomatic analysis revealed that each of the biomarkers corresponded to certain combinations of the results (patterns). The formation of patterns is possible for any number of characteristics, but in this case, a combination of three of them was sufficient to obtain significant differences.

Table 2

Concentrations of the MMP / TIMP system parameters in patients with tuberculoma, *Me* [Q_1; Q_3]

Analytes	Patients with tuberculoma	Healthy controls	*p*
MMP-1Log, ng / ml	1.74 [1.31;2.30]	1.17 [0.89;1.72]	0.002
MMP-8Log, ng / ml	3.27 [2.64;3.94]	2.58 [2.22;2.70]	0.003
MMP-9, ng / ml	1,638.00 [50.80;2,557.69]	71.99 [51.33;73.94]	0.00004
TIMP-1Log, ng / ml	6.72 [6.58;6.89]	6.66 [6.55;6.80]	0.05
MG, nmol / min	1.70 [1.40;2.16]	3.00 [2.46;3.28]	0.00003

Note. The level of statistical significance compared to healthy controls – *p* (Mann–Whitney *U*-test).

Table 3

Concentration of the MMP / TIMP system parameters depending on the clinical and radiological characteristics of inflammation in patients with tuberculoma, *Me* and *MeLog* [Q_1; Q_3]

Pathological changes		Аналиты				
		MMP-1Log, ng / ml	MMP-8Log, ng / ml	MMP-9, ng / ml	TIMP-1Log, ng / ml	MG, nmol / min
Signs of necrosis	1	1.57 [1.02; 2.09]	3.15 [2.59; 3.83]	1721.00 [950.00; 2665.00]	6.68 [6.57; 6.84]	1.94 [1.35; 2.25]
	2	1.85 [1.46; 2.37]	3.50 [3.21; 3.93]	1771.00 [950.00; 2665.00]	6.77 [6.60; 6.93]	1.90 [1.57; 2.10]
Number of tuberculomas	1	1.84 [1.41; 2.23]	3.12 [2.73; 3.50]	1544.00 [924.00; 2343.00]	6.74 [6.61; 6.92]	1.84 [1.38; 2.10]
	2	1.96 [1.48; 2.46]	3.39 [3.07; 3.98]	1905.00 [1140.00; 2643.00]	6.71 [6.59; 6.89]	2.04 [1.43; 2.25]
External respiration disorders	1	1.54 [1.02; 1.96]	3.51 [3.36; 3.64]	1823.00 [1079.00; 2638.00]	6.74 [6.57; 6.98]	2.09 [1.35; 2.78]
	2	1.89 [1.38; 2.74]	3.49 [3.07; 3.89]	1769.00 [1100.00; 2185.00]	6.68 [6.59; 6.83]	1.96 [1.43; 2.16]
Catarrhal bronchitis	1	1.84 [1.41; 2.24]	3.60 [2.77; 4.44]	1355.00 [761.00; 2036.00]	6.58 [6.52; 6.82]	2.09 [1.35; 2.78]
	2	1.80 [1.36; 2.27]	3.21 [2.68; 3.76]	1778.00 [1058.00; 1778.00]	6.75 [6.65; 6.93]	1.96 [1.43; 2.16]
Tobacco smoking	1	1.74 [1.01; 2.46]	3.03 [2.72; 3.42]	1574.00 [651.00; 2447.00]	6.59 [6.54; 6.78]	2.30 [1.59; 2.99]
	2	1.85 [1.56; 2.26]	3.53 [3.05; 3.98]	1863.00 [1186.00; 2376.00]	6.73 [6.59; 6.93]	1.98 [1.50; 2.20]

Note. 1 – no signs of necrosis, single tuberculomas, no external respiration disorders, no catarrhal bronchitis, non-smoking patients; 2 – signs of necrosis, multiple tuberculomas, external respiration disorders, catarrhal bronchitis, smoking patients.

Stratified sampling based on the levels of collagenase MMP-1 and gelatinase MMP-9 allowed to identify pattern 1 – a combination of the number of tuberculomas, external respiration disorders, and CB ($p = 0.01$). Two-fold differences in MMP-1Log made it possible to differentiate a more severe subgroup of patients with multiple tuberculomas in combination with either external respiration disorders or CB. The median MMP-1 ($n = 37$) in the group of patients with severe disease reached 1.96 ng / ml (1.66; 1.9), while in the group with moderate disease ($n = 35$), it was 1.23 ng / ml (0.86; 1.56).

Similarly, in the group with severe disease, *Me* MMP-9 was 2,008 ng / ml (1,148; 2,648), while in the group with moderate disease, it was 1,351 ng / ml (874; 1,971).

It is assumed that the progression of tuberculoma increases as the volume of affected lung tissue enlarges. The formed pattern suggests that a conclusion about the progression of inflammation based solely on differences in its prevalence is not always correct According to pattern 1, an increase in the volume of morphological changes in the lung parenchyma becomes clinically significant when accompanied by external respiration disorders. The present study established a direct correlation between external respiration disorders and the volume of lung lesions (r = 0.27; p = 0.03, Spearman's rank correlation coefficient), which is consistent with literature data indicating a significant relationship between changes in ventilation and gas exchange parameters of the lungs in tuberculoma and the severity of such changes as the volume of the largest cavity, total volume of necrotic areas, presence of pleural involvement, and the prevalence of seeding foci [13].

The composition of pattern 1 also indicates a significant negative impact on the course of the primary infection in the lungs of non-specific inflammatory responses in the bronchial mucosa. CB, impairing the bronchial drainage function and changing the microcirculation in the affected bronchopulmonary segments, contributes to the aggravation of the process [14]. Differences in the concentration of MMP-1Log allowed to form pattern 2, which combined the characteristics of the total lesion volume, the total area of necrosis, and the presence of CB (p = 0.0017).

The group with a higher concentration of proteinase included patients (n = 42) who had multiple tuberculomas with the presence of CB or areas of necrosis. In this group, the median MMP-1Log was 6.63 ng / ml (3.62; 9.83). In the group of patients who had no areas of necrosis or no combination of multiple tuberculomas with CB (n = 19), the median MMP-1Log was 2.5 times lower, amounting to 2.56 ng / ml (1.56; 4.09). The significance of pattern 2 confirms the relevance of the dynamic assessment of changes in the volume of affected tissue used in clinical practice as one of the criteria for assessing the course of the disease.

It is known that tuberculomas with areas of necrosis progress more frequently than those without them (44.7 vs. 10.5%). Moreover, small foci tend to further decrease in size, while large tuberculomas are primarily characterized by the preservation of necrosis with an increase in its volume. The progression of tuberculomas is caused by lysis of caseous necrosis with subsequent cavernization of tuberculoma and bronchogenic dissemination of its contents [15]. Destruction of tuberculoma occurs as a result of its exposure to proteolytic enzymes, and the leading role in the formation of a caseous focus belongs to MMP-1 [16].

Thus, the composition of patterns formed during the analysis of subgroups associated with statistically significant differences in MMP-1Log and MMP-9 levels represents the most unfavourable combination of clinical and radiological characteristics of tuberculoma in terms of the clinical course of the disease. Such characteristics as the presence of multiple tuberculomas with external respiration disorders and inflammation of the tracheobronchial tree, as a rule, reflect the progression of specific inflammation.

Differences in the concentration of neutrophil collagenase (MMP-8) allowed for the formation of pattern 3, based on a combination of at least two of the characteristics discussed. For example, in the group of smoking patients with multiple foci (n = 39), the concentration of proteinase reached 3.83 ng / ml (3.21; 4.46) in contrast to a more favourable group (n = 9) where such factors were absent. MMP-8Log in this case was 1.2 times lower and amounted to 3.09 ng / ml (2.73;3.50).

Tobacco smoking is a risk factor that aggravates the severity of the disease, contributing to the prolongation of non-specific inflammation, and is one of the causes of irreversible external respiration disorders [17]. It was found that the patients of the subgroup with pattern 3 differed by 1.2 times from the rest of the patients in the Gaensler index (r = 0.27; p = 0.02), the main forced expiratory maneuver parameter, whose decrease is crucial in the diagnosis of lower airway obstruction.

The found relationship between the total volume of foci and the number of segmented neutrophils (r = 0.60; p = 0.04), which are the source of MMP-8, is in agreement with literature data on the increase in the number of peripheral blood neutrophils in patients with a progressive course of the disease as compared to its regressive and stable course [18].

Changes in the level of TIMP-1 and MG allowed for the formation of pattern 4, determined by the influence of a combination of CB and tobacco smoking (p = 0.004). It was found that in the presence of both characteristics, the level of TIMP-1Log was significantly higher (p = 0.004), amounting to 6.77 ng / ml (6.67;6.94), whereas in the absence of these factors, the concentration of TIMP-1Log was 6.52 ng / ml (6.47;6.67). A similar 1.5-fold decrease

was found for MG (p = 0.04). The activity of the inhibitor was reduced to 2.00 nmol / min (1.50; 2.25) in the more severe subgroup according to clinical and radiological characteristics, while in other patients, it remained at the reference level of 2.61 nmol / min (2.10; 3.09).

The validity of the composition of pattern 4 is explained by the literature data on the presence of bronchial pathology of a non-specific genesis in patients with smoking experience of more than 10 years, the so-called smoker's cough [19]. The revealed combination characterizes failure of inhibitory protection and corresponds to endoscopic presentation of non-specific CB of high prevalence.

Analyzing all 4 patterns, it should be noted that their composition characterizes both specific (necrosis, lesion volume) and non-specific (CB and tobacco smoking) components of inflammation, which indicates the nonlinear nature of the relationship between the MMP / TIMP system parameters and manifestations of the process intensity according to clinical and radiological criteria. Thus, changes in the parameters of the MMP / TIMP system can be considered as objective laboratory biomarkers for assessing the clinical course of specific inflammation in pulmonary tuberculoma.

CONCLUSION

The use of the symptomatic analysis made it possible to form four patterns, corresponding to different levels of MMPs in the blood, from the characteristics used to assess the clinical course of the disease. An increase in the concentration of MMP-1Log and MMP-9 in peripheral blood may be a predictor of the progression of multiple tuberculomas in the presence of necrosis and bronchogenic dissemination (patterns 1, 2). Changes in the levels of MMP-8, TIMP-1 or MG emphasize the significance of the permanent effect of non-specific inflammation components on the assessment of the process severity and do not exclude the possibility of its progression (patterns 3 and 4). The integrative approach combining the evaluation of serum protein biomarkers with the results of clinical and radiological studies is a highly promising non-invasive tool for predicting the direction of development of pulmonary tuberculoma without bacterial excretion.

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Authors' contribution

Esmedlyaeva D.S. – conception and design, preparation of the samples, collection of the material, carrying out biochemical studies; literature review; analysis and interpretation of the data; drafting of the manuscript. Alekseeva N.P. – statistical processing of the results; drafting of the article. Dyakova M.Ye. – carrying out biochemical studies. Karostik D.V. – carrying out radiological studies. Grigoriev I.V. – translation of the article, conception of the article. Sokolovich E.G. –generation of the idea of the study, conception and design of the study; scientific editing; final approval of the manuscript for publication.

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