UDK: 616.24-002:616.72-002

EARLY DETECTION OF SUBCLINICAL INTERSTITIAL LUNG DISEASE IN RHEUMATOID ARTHRITIS USING HIGH-RESOLUTION CT, PULMONARY FUNCTION TESTING, AND CYTOKINE PROFILING

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Abstract: This study assessed subclinical interstitial lung involvement in patients with rheumatoid arthritis using clinical, functional, radiological, and cytokine parameters. 61 patients were examined, including 15 with subclinical, 25 with clinical, and 21 without pulmonary involvement. High-resolution computed tomography identified ground-glass, reticular, traction bronchiectatic, and honeycomb changes. Diffusing capacity was significantly reduced in subclinical disease compared with patients without lung involvement. Elevated vascular endothelial growth factor may indicate a marker of pulmonary fibrosis progression and support earlier clinical recognition of disease.

Keywords: rheumatoid arthritis; interstitial lung disease; high-resolution computed tomography; diffusing capacity; vascular endothelial growth factor.

РАННЯЯ ДИАГНОСТИКА СУБКЛИНИЧЕСКОГО ИНТЕРСТИЦИАЛЬНОГО ПОРАЖЕНИЯ ЛЕГКИХ ПРИ РЕВМАТОИДНОМ АРТРИТЕ С ИСПОЛЬЗОВАНИЕМ КТ ВЫСОКОГО РАЗРЕШЕНИЯ, ИССЛЕДОВАНИЯ ФУНКЦИИ ВНЕШНЕГО ДЫХАНИЯ И ЦИТОКИНОВОГО ПРОФИЛЯ

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Аннотация: В исследовании оценено субклиническое интерстициальное поражение легких у пациентов с ревматоидным артритом с учетом клинических, функциональных, рентгенологических и цитокиновых

показателей. Обследован 61 пациент: 15 с субклиническим, 25 с клиническим поражением легких и 21 без легочной патологии. Компьютерная томография высокого разрешения выявила изменения по типу «матового стекла», ретикулярную исчерченность, тракционные бронхоэктазы и признаки «сотового легкого». Диффузионная способность легких была снижена при субклиническом течении по сравнению с пациентами без поражения легких. Повышение VEGF может иметь прогностическое значение для оценки фиброзирования легочной ткани.

Ключевые слова: ревматоидный артрит; интерстициальное поражение легких; компьютерная томография высокого разрешения; диффузионная способность легких; VEGF.

Introduction: Rheumatoid arthritis is a systemic autoimmune disease characterized primarily by persistent synovial inflammation, but its pathological process may extend to the respiratory system. Interstitial lung involvement is an important extra-articular manifestation because structural abnormalities can develop before obvious respiratory symptoms. High-resolution computed tomography can reveal pulmonary changes that remain undetected by conventional radiography or routine clinical examination. This creates a diagnostic challenge in subclinical disease, when patients may have limited symptoms but early impairment of gas transfer. Diffusing capacity of the lungs is therefore potentially useful for identifying functional abnormalities early. Autoimmune markers and inflammatory mediators may provide additional information about pulmonary injury. Anti-cyclic citrullinated peptide antibodies and rheumatoid factor are relevant because seropositivity has been associated with extra-articular manifestations, while cytokines may reflect inflammatory and fibrotic activity. Vascular endothelial growth factor is of particular interest because vascular remodeling may participate in pulmonary fibrosis. The source study compared rheumatoid arthritis patients with subclinical interstitial pulmonary involvement, clinically manifest interstitial involvement, and no pulmonary abnormalities. High-

resolution computed tomography, pulmonary function testing, serological investigations, and cytokine profiling were used to characterize these groups. This integrated combined approach may clarify relationships between structural abnormalities, impaired diffusion, and inflammatory mediators and may assist the earlier identification of patients at risk of progressive pulmonary fibrosis.

Aim of the study: To compare the clinical, functional, radiological, and cytokine characteristics of rheumatoid arthritis patients with subclinical and clinically manifest interstitial pulmonary involvement and those without pulmonary abnormalities, with particular attention to early indicators of pulmonary fibrosis.

Materials and methods. The study included 61 inpatients with rheumatoid arthritis diagnosed according to the 1987 American College of Rheumatology criteria. High-resolution computed tomography divided participants into three groups: 15 patients with ground-glass pulmonary changes representing subclinical interstitial involvement, 25 with reticular changes, traction bronchiectases or honeycomb-type abnormalities representing clinical involvement, and 21 without pathological pulmonary findings. Groups were comparable in sex and age and mainly had radiographic stages II–III and functional classes I–II. Rheumatoid arthritis activity was assessed using DAS28. Radiographs of the hands, feet, and chest were performed; chest CT used 0.65-mm slices. Pulmonary function was measured by body plethysmography, including forced vital capacity, forced expiratory volume in one second, total lung capacity, FEV1/FVC ratio, and lung diffusing capacity. Diffusing capacity was determined using the single-breath method. Serum IgM rheumatoid factor was measured by immunonephelometry, and anti-cyclic citrullinated peptide antibodies by immunochemiluminescence. Serum concentrations of 27 cytokines were assessed in 15 patients with subclinical and 25 with clinical interstitial pulmonary involvement using multiplex xMAP technology. Mediators included interleukins, interferon-gamma, chemokines, platelet-derived growth factor BB, tumor necrosis factor-alpha, and vascular endothelial growth factor. Smoking, occupational hazards, bronchopulmonary

disease, rheumatoid nodules, polyneuropathy, and Sjogren syndrome were considered. Statistical analysis used Statistica 6.0. Mann–Whitney and Kruskal–Wallis tests were applied for non-normally distributed variables, and Spearman correlation for associations. Statistical significance was accepted at $p<0.05$.

Results. High-resolution CT identified pulmonary abnormalities in 40 of 61 patients, whereas 21 had no pathological findings. Fifteen patients had subclinical ground-glass changes, while 25 had clinical reticular abnormalities, traction bronchiectases, or honeycomb-type changes. Respiratory manifestations were most prominent clinically: cough occurred in 24%, sputum production in 20%, dyspnea in 16%, and crackles in 64%. Three subclinical patients also had crackles. Patients with pulmonary involvement had a higher smoking index than those without lung disease ($p<0.05$). Rheumatoid nodules, polyneuropathy, and Sjogren syndrome were more frequent with pulmonary involvement ($p<0.005$, $p<0.005$, and $p<0.05$). Disease duration was longer in the clinical group than without pulmonary involvement ($p<0.05$), while rheumatoid arthritis onset occurred later in patients with lung disease ($p<0.05$). Diffusing capacity was significantly reduced in subclinical involvement versus patients without pulmonary disease ($p<0.05$). In clinical disease, diffusing capacity and total lung capacity were lower than without pulmonary abnormalities ($p<0.005$ and $p<0.05$). Median diffusing capacity was 72%, 62%, and 84% in the subclinical, clinical, and unaffected groups, respectively. Other respiratory function parameters did not differ significantly in subclinical disease, supporting early selective impairment of gas transfer before overt symptoms develop. Vascular endothelial growth factor was significantly higher in subclinical than clinical disease ($p<0.05$). Interleukin-10, interferon-gamma, and RANTES were higher in clinical disease ($p<0.008$, $p<0.0003$, and $p<0.03$). Interleukin-7, -12, -13, -15, -17, and platelet-derived growth factor BB tended to be higher subclinically, without significant differences.

Conclusions: Subclinical interstitial pulmonary involvement in rheumatoid arthritis may occur with limited symptoms but detectable structural and functional

abnormalities. Ground-glass changes were accompanied by reduced diffusing capacity: 72% in subclinical, 62% in clinical involvement, versus 84% without pulmonary disease. Clinical disease also showed reduced total lung capacity. Higher smoking exposure and extra-articular manifestations accompanied pulmonary involvement. Higher vascular endothelial growth factor in subclinical disease and increased interleukin-10, interferon-gamma, and RANTES in clinical disease indicate inflammatory profiles. High-resolution CT and pulmonary function testing have complementary diagnostic value for recognizing pulmonary involvement. Vascular endothelial growth factor may be a marker of fibrotic progression

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