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CYTOKINE IMBALANCE AND INTERSTITIAL LUNG INVOLVEMENT IN RHEUMATOID ARTHRITIS: CLINICAL AND DIAGNOSTIC ASSOCIATIONS

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Abstract: This study investigated serum cytokine profiles in patients with rheumatoid arthritis with and without interstitial lung involvement. The study included 20 patients with rheumatoid arthritis and interstitial lung involvement, 30 patients without lung involvement, and 28 healthy donors. Serum concentrations of 27 cytokines were measured using multiplex xMAP technology, while lung involvement was verified by computed tomography. Patients with interstitial lung involvement demonstrated significantly higher IL-10 and IFN-γ levels, while VEGF concentrations were lower than in healthy donors. ROC analysis identified RANTES, IFN-γ, and IL-8 as the most informative cytokines, with AUC values of 1.00, 0.98, and 0.92, respectively.

Keywords: rheumatoid arthritis; interstitial lung involvement; cytokines; IFN-γ; RANTES.

ДИСБАЛАНС ЦИТОКИНОВ И ИНТЕРСТИЦИАЛЬНОЕ ПОРАЖЕНИЕ ЛЕГКИХ ПРИ РЕВМАТОИДНОМ АРТРИТЕ: КЛИНИЧЕСКИЕ И ДИАГНОСТИЧЕСКИЕ ВЗАИМОСВЯЗИ

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Аннотация: В исследовании изучен сывороточный цитокиновый профиль у пациентов с ревматоидным артритом с интерстициальным поражением легких и без него. В исследование включили 20 больных ревматоидным артритом с интерстициальным поражением легких, 30 пациентов без

поражения легких и 28 здоровых доноров. Концентрации 27 цитокинов определяли методом мультиплексного анализа xMAP, а наличие легочного поражения верифицировали с помощью компьютерной томографии. При интерстициальном поражении легких выявлено значимое повышение уровней IL-10 и IFN-γ, тогда как концентрация VEGF была ниже по сравнению со здоровыми донорами. ROC-анализ показал наиболее высокую диагностическую информативность RANTES, IFN-γ и IL-8 с площадью под кривой 1,00, 0,98 и 0,92 соответственно.

Ключевые слова: ревматоидный артрит; интерстициальное поражение легких; цитокины; IFN-γ; RANTES.

Introduction: Rheumatoid arthritis is a systemic autoimmune disorder whose manifestations extend beyond joints and may involve the respiratory system. Interstitial lung involvement is an important extra-articular complication because immune activation contributes to pulmonary inflammation and fibrosis. The mechanisms remain incompletely defined, particularly the contribution of circulating cytokines to interstitial abnormalities. Cytokines regulate communication between immune cells, fibroblasts, endothelial cells, and pulmonary tissue components, making their concentrations potentially useful for characterizing disease phenotypes. Patients with rheumatoid arthritis and pulmonary involvement may demonstrate a distinct balance between Th1- and Th2-associated mediators. However, interpretation of individual cytokines is difficult because rheumatoid arthritis itself produces systemic inflammatory activation. Therefore, comparison with rheumatoid arthritis patients without lung involvement and healthy individuals is important for identifying markers associated with pulmonary disease. Multiplex technologies permit simultaneous measurement of numerous cytokines from serum. IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IFN-γ, RANTES, and VEGF are of particular interest because they participate in immune regulation, leukocyte recruitment, vascular processes, or tissue remodeling. High-resolution computed tomography can establish interstitial lung

involvement and provide an objective basis for comparing cytokine profiles. A combined radiological and immunological approach may clarify associations between systemic inflammation and pulmonary manifestations of rheumatoid arthritis. Such characterization could support identification of patients requiring respiratory assessment and contribute to biomarker development and clinical significance.

Aim of the study: To evaluate cytokine profiles in patients with rheumatoid arthritis with and without interstitial lung involvement and determine their potential diagnostic significance using comparative and ROC analyses.

Materials and methods. The study included 78 participants divided into three groups: 20 patients with rheumatoid arthritis and interstitial lung involvement, 30 patients with rheumatoid arthritis without lung involvement, and 28 healthy donors. The groups were comparable in sex and age. Rheumatoid arthritis was diagnosed according to the 1987 American College of Rheumatology criteria, and disease activity was assessed using DAS28. Most patients had prolonged disease, seropositivity for rheumatoid factor and anti-cyclic citrullinated peptide antibodies, high inflammatory activity, radiographic stages II–III, and predominantly functional class II. Serum concentrations of 27 cytokines were measured using multiplex xMAP technology on a Bio-Plex200 analyzer. The panel included IL-1β, IL-1 receptor antagonist, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, eotaxin, FGF2, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF-BB, RANTES, TNF-α, and VEGF. Interstitial lung involvement was verified by lung computed tomography using a GE Light Speed VCT scanner with 0.65-mm section thickness. Pulmonary function testing included diffusing capacity, forced vital capacity, forced expiratory volume in one second, total lung capacity, and the FEV1/FVC ratio, measured with a MasterScreen Body system. Statistical analysis was performed with Statistica 6.0. Normally distributed variables were compared using a t-test; nonparametric variables were analyzed using Mann–Whitney and Kruskal–Wallis tests. Spearman correlation assessed

associations, while ROC analysis evaluated diagnostic performance. Differences were considered statistically significant at $p<0.05$.

Results. Cytokine analysis demonstrated broad immune activation in rheumatoid arthritis. Compared with healthy donors, both rheumatoid arthritis groups had significantly higher IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12, IL-15, eotaxin, G-CSF, GM-CSF, IFN-γ, MIP-1β, PDGF-BB, RANTES, and TNF-α concentrations. Patients with interstitial lung involvement had higher IL-4 and IP-10 than the other groups, although statistical significance for these differences was reached only versus healthy donors ($p=0.04$ and $p=0.001$). IL-10 was significantly higher in patients with lung involvement than in rheumatoid arthritis without lung disease and healthy donors ($p=0.008$ and $p=0.0001$). IFN-γ showed an even stronger difference, with $p=0.0003$ versus rheumatoid arthritis without lung involvement and $p=0.0001$ versus healthy donors. RANTES was also increased in the lung involvement group compared with rheumatoid arthritis without pulmonary disease ($p=0.03$) and healthy donors ($p=0.0001$). VEGF was lower in patients with interstitial lung involvement than in healthy donors ($p=0.05$). ROC analysis identified several cytokines with significant diagnostic value. IL-5 had an AUC of 0.79, IL-6 0.89, IL-7 0.87, IL-8 0.92, IL-10 0.77, IL-12 0.92, IP-10 0.72, MIP-1β 0.80, IFN-γ 0.98, and RANTES 1.00; $p=0.001$ for all markers. RANTES demonstrated 95% sensitivity and 100% specificity, while IFN-γ showed 95% sensitivity and 96% specificity. IL-8 reached 91% sensitivity and 82% specificity. No significant correlation was found between baseline cytokine concentrations and DAS28. IL-1β, IL-1Ra, IL-5, IL-12, G-CSF, and eotaxin correlated positively with rheumatoid factor levels in affected patients.

Conclusions: Patients with rheumatoid arthritis and interstitial lung involvement demonstrated a distinct cytokine pattern characterized by increased IL-10, IFN-γ, and RANTES and reduced VEGF compared with relevant control groups. ROC analysis identified RANTES, IFN-γ, and IL-8 as the most informative markers, with AUC values of 1.00, 0.98, and 0.92. The findings support a mixed Th2 and

Th1 immune response in pulmonary disease. Cytokine profiling combined with computed tomography may improve recognition of interstitial lung involvement. RANTES and IFN-γ warrant further prospective evaluation as potential biomarkers for early detection and clinical risk stratification in rheumatoid arthritis and monitoring of pulmonary disease progression.

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