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Cytokine Profile in Patients With Rheumatoid Arthritis

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Abstract: A possible relationship between markers of anemia, cytokine status, and left ventricular diastolic dysfunction (LVEF) was studied in patients with rheumatoid arthritis (RA). Serum levels of tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10), erythropoietin (EPO), and echocardiographic markers of LVEF were studied in 85 patients. We have established the presence of an imbalance between TNF-α and IL-10, negative associations between TNF-α and EPO, as well as between TNF-α and the LDLF E/A index. Thus, anemia and LVEF in RA are associated with the influence of the proinflammatory cytokine TNF-α.

Key words: anemia, cytokines, erythropoietin, diastolic dysfunction.

INTRODUCTION

Rheumatoid arthritis (RA) is one of the most common and socially significant rheumatic diseases with a population frequency of 0.6 to 1.3%, accompanied by early disability. Recently, the attention of researchers has been attracted by the high frequency of comorbid cardiovascular manifestations of RA, associated with the accelerated development of endothelial dysfunction, anemia, chronic inflammation, and the course of the autoimmune process. It is important that even significant damage to the heart and blood vessels in RA is usually latent and does not attract the attention of patients and attending physicians, which leads to late diagnosis and inadequate therapy. A number of studies have shown that the traditional risk factors for atherosclerosis – age, gender, hyperlipidemia, hypertension – do not adequately reflect the course of coronary heart disease and hypertension in RA, and an increase in cardiovascular morbidity and mortality occurs in the early stages of the disease, especially in the seropositive variant in women. Data on the diagnostic value of determining diastolic blood pressure disorders are important. left ventricular function in this category of patients as a preclinical marker of myocardial insufficiency. Anemia of chronic inflammation, which is observed in the active phase in the majority of RA patients, is currently considered as the most important prognostic factor of life expectancy, at the same time, the mechanisms of its development and approaches to correction remain not fully established. In experimental and isolated clinical studies, there are indications of activation of proinflammatory cytokines in patients with RA and its relationship with the development of anemia. The anemic factor is also traditionally associated with hemodynamic changes in the form of increased cardiac output, decreased peripheral vascular resistance due to the development of tissue hypoxia, and impaired blood viscosity. At the same time, there are almost no studies that would directly compare the anemia syndrome and the severity of cytokine activation with hemodynamic parameters in patients with RA. The purpose of the study was to study the possible interrelationships and interactions of anemia syndrome, cytokine profile, systolic and diastolic functions of the left ventricle in patients with RA.

MATERIALS AND METHODS OF RESEARCH

85 patients with seropositive RA (10 men, 75 women) of moderate to high activity were examined at the age of 48.1±10.4 years, with a disease duration of 18.3±8.6 years. The diagnosis of RA was established in accordance with the criteria of the American Rheumatological Association and the clinical recommendations of the Association of Rheumatologists of Uzbekistan. The control group

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consisted of 20 practically healthy individuals (3 men, 17 women) with an average age 46.3±6.4 years. RA patients with an established diagnosis of amyloidosis, the presence of proteinuria, and chronic renal failure of any stage were excluded from the study. The hemogram parameters, the concentration of C-reactive protein (CRP), rheumatoid factor (RF), and total blood cholesterol were evaluated using an automatic biochemical analyzer. The concentration of human erythropoietin-α, tumor necrosis factor- (TNF-), and interleukin-10 (IL-10) levels was studied using a Statfax 2100 enzyme immunoassay analyzer using reagent kits for enzyme immunoassay manufactured by the Protein Contour company. Systolic and diastolic functions of the left ventricle were studied echocardiographically according to generally accepted methods. Statistical data processing was carried out using the Statistica 6.0 program using nonparametric methods. The data is presented as a median (25th; 75th percentile), the differences between the groups were assessed using criteria Kruskall-Wallis and Mann-Whitney. Spearman's rank correlation coefficient was determined for correlation analysis.

THE RESULTS AND THEIR DISCUSSION

The parameters of the hemogram and the concentration of traditional serum markers of inflammation, the studied cytokines and erythropoietin-x. Analysis of the data obtained allowed us to establish the presence of anemia in 58 patients with RA (69%), with a hemoglobin level of 100-120 g/l registered in 51, hemoglobin values of 80-100 g/l were found in 7 patients. 27 patients with RA (31%) had no signs of anemia. The levels of CRP and rheumatoid factor varied unidirectionally and turned out to be higher than in the control group both without and with anemia. The concentration of erythropoietin was found to be elevated in the group of RA patients without anemia, it was almost twice as high as in the control group. The group with anemia showed a lower concentration of endogenous erythropoietin compared to both the control group and the group without anemia. The results obtained probably indicate that when The activation of the erythropoietin link outstrips the clinically pronounced signs of anemia, and if it is present, erythropoiesis is inhibited. When studying TNF- and IL-10 concentrations, increased values were determined both in the group with and without anemia compared with the control group. In the group of patients with anemia, there was a more than tenfold increase in the concentration of both TNF-and IL-10. When assessing the balance of pro- and anti-inflammatory cytokines, determined by TNF- /IL-10, it turned out that in the group of patients with anemia, there was a shift towards the pro-inflammatory cytokine TNF- compared with the control group and the group without anemia. We have identified an inverse correlation between the concentration of endogenous erythropoietin and tumor necrosis factor-α in the group of patients with anemia (r=-0.62; p=0.03). The same relationship remained between the TNF-/IL-10 index and the concentration of erythropoietin (r=-0.42; p=0.04). The revealed relationships at the clinical level indicate a functional relationship between the severity of anemia and the degree of pro-inflammatory activation in RA, as well as the importance of cytokine imbalance in the development of anemia. No differences in systolic function were determined in the studied subgroups of RA patients when analyzing echocardiogram parameters. At the same time, a violation of diastolic function, estimated by The E/A ratio was found in 68% of RA patients with anemia. In the group of healthy individuals, the median relationship is The E/A was 1.25 (0.51; 1.8) and practically did not differ from the values of this indicator in patients with RA without anemia. However, in RA patients with anemia, this indicator was significantly reduced, amounting to 0.74 (0.3; 1.2) conventional units (p=0.04). We also determined a negative relationship between the E/A index characterizing diastolic dysfunction of the left ventricle and TNF concentration (r=-0.41; p=0.04) in RA patients with anemia, which indicates the important role of this proinflammatory cytokine in the development of myocardial damage in anemia on the background of RA.

CONCLUSIONS

Thus, the majority of the examined patients with RA had clinical manifestations of anemia with a decrease in the synthesis of endogenous erythropoietin and a greater severity of the proinflammatory cytokine response. The negative effect of TNF on erythropoietin levels and the development of diastolic dysfunction in RA patients has been established. The interdependencies we have identified between TNF levels , erythropoietin concentrations, and left ventricular diastolic dysfunction indicate

the influence of these factors. It affects the development of cardiac decompensation in RA, which probably requires not only exposure to the pro-inflammatory cytokine link, but also timely correction of the anemia syndrome.

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