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THE CLINICAL SIGNIFICANCE OF INTERLEUKIN-4 IN SYSTEMIC SCLERODERMA

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Abstract
Goal. To study the relationship of serum interleukin-4 (IL-4) levels with visceral pathology, the nature of the course and clinical forms of SSD.
Materials and methods. IL-4 was determined in the sera of 40 patients with SSD by indirect solid-phase enzyme immunoassay (ELISA).
Results. The level of IL-4 in the range of 10-1000 pg/ml was detected in 12 out of 40 patients with SSD (30%). The distinctive features of this group of patients were a shorter duration of the disease, progression of cutaneous fibrosis and visceral pathology by the time of examination and a tendency to a higher incidence of pulmonary fibrosis. There were no significant differences in the lesion of other internal organs, as well as the dependence of the IL-4 content on the clinical forms and course of the disease. In patients with an increase in IL-4 in the blood showed higher levels of CIC, u-globulins, while the content of acute-phase reactants was lower than in the rest of the group.
Conclusion. The established association of serum IL-4 levels with the activity of the fibrous process in SSD requires confirmation in prospective studies.

Keywords: interleukin-4. T lymphocytes, fibrosis, activity, systemic scleroderma.

Introduction

Systemic scleroderma (SSD) is an autoimmune disease characterized by excessive synthesis of collagen and other components of the intercellular matrix by fibroblasts, leading to fibrosis skin and internal organs. Although the pathogenesis of the disease is largely unclear, the leading role of T cell immune mechanisms in the initiation and progression of the fibrous process is generally recognized. The basis of these disorders is dysregulation in the Thl and TH2 lymphocyte system with hyperreactivity of Th2 cells secreting fibrogenic cytokines. The latter are able to activate fibroblasts, causing their migration, proliferation and excessive synthesis of matrix proteins. Interleukin-4 (IL-4) is one of the Th2-dependent cytokines, presumably involved in the development of sclerodermic fibrosis. Its overexpression It is found in the skin, mononuclear cells of peripheral blood and bronchoalveolar lavage cells of patients with SSD. The stimulating effect of IL-4 on collagen synthesis by fibroblasts of sclerodermically altered skin, activation of fibronectin and tenascin synthesis has been proven. The key role of IL-4 in the development of the disease is also confirmed by experimental data on the possibility of preventing cutaneous fibrosis in Tsk/mice (experimental model of SSD) by artificially induced mutation in the IL-4 receptor gene, leading to loss of fibroblast sensitivity to this cytokine.

The clinical aspect of the study of IL-4 in SSD is represented by isolated studies, the data obtained are contradictory both in relation to the presence of this cytokine in the blood of patients with SSD and associations with clinical manifestations of the disease. The purpose of this work was to study the clinical significance of IL-4 in patients with SSD with various forms, variants of the course and stages of the disease.

MATERIALS AND METHODS OF RESEARCH

The study included 40 patients with SSD: 36 wives and 4 husbands aged 24 to 72 years, on average 50.33±12.37 years, with acute (14), subacute (7) and chronic (19) course of the disease. In 29 patients , there was a limited form of SSD (LSD) and in 10 - diffuse (dSSD). All patients with dSSD and 26 lSSD met the diagnostic criteria of ARA, 1980. The duration of the disease (from the onset of scleroderma skin lesion) averaged 8.22±7.1 years, in 12 people (30%), the duration of SSD did not exceed 3 years (early stage). For To determine the severity and prevalence of skin induration, a skin score was used in the modification of M.B.Kaheleh 1986 (a total score of skin density in 26 skin zones on a 3-point scale). The assessment of the dynamics of cutaneous fibrosis in the majority of patients (32 people) was carried out by comparing the skin score at the time of the study with the results of previous hospitalization (for a period of 6-12 months), in 8 patients for the first time The assessment of those admitted to the IR was carried out from the words of the patient according to the change in the density and prevalence of skin lesions over the previous month. In addition to the clinical characteristics of cutaneous, vascular and visceral pathology, immunological (CEC by nephelometry, RF by latex agglutination, ANF by immunofluorescence method on histological sections of rat liver and on Hep-2 cell culture with titer and type of glow registration, anticentromeric antibodies, antibodies to Scl-70, immunoglobulins of classes G, and, M by the Mancini method) and general clinical blood parameters (shaped elements, ESR, C-reactive protein, total protein and protein fractions, creatinine, CK). IL-4 was determined in the sera of patients by indirect solid-phase enzyme immunoassay (ELISA) using a set of ProCon IL-4 reagents. The results were recorded using a spectrophotometer (Dynatech) at a wavelength of 450 nm. According to the literature data, the upper limit of the norm of serum IL-4 is 1 Opg/ml. In the sera of healthy individuals, IL-4 in this concentration occurs in 0-1% of cases. Statistical processing of the results was carried out using the t-test, %2 - test and correlation analysis (Pearson correlation coefficient).

THE RESULTS AND THEIR DISCUSSION

All patients had a characteristic SSD peripheral and visceral symptoms, including skin lesions (dense edema - in 24 patients, induration - in 14, average skin score - 8.1 ± 7.3 points), vascular pathology (Raynaud's syndrome in all patients, trophic vascular disorders - in 24), damage to the musculoskeletal system (arthritis - 9, myositis - 2, muscle weakness - 5) and internal organs (scleroderma lesion of the esophagus -31, lungs - 29, heart - 24, kidneys - 1, pulmonary hypertension - 8). Progression of cutaneous fibrosis was noted in 10 patients with visceral pathology in 11. 22 patients (55%) included in the study were treated with prednisone (22), D-penicillamine (12), cytotoxic drugs (6), aminoquinoline drugs (3), NSAIDs (5) patients; extracorporeal therapies (plasmapheresis) were used in 2 patients.

ANF in the study on Hep-2 cell culture it was detected in 90% of patients. In all cases, a speckled type of glow was noted, in 27% there was a combination of it with a homogeneous one, in 6% with a nucleolar one. 30% of patients were found to have SSD-specific autoantibodies: Scl-70 (17%) or anticentromeric antibodies (13%). They are similar (in 5 cases according to the type of diffuse pneumofibrosis). The progressive course of the disease was noted in 58% of patients. In 4 out of 5 patients, whose condition is clinically assessed as stable, there has been an increase in laboratory activity over the past year. Half of the patients in this group were admitted to the Institute of Rheumatology for the first time with an exacerbation of SSD due to the absence or ineffectiveness of therapy. Most of them were prescribed corticosteroids, cytotoxics and/or Dpenicillamine at the clinic. In a comparative analysis, it was noted that IL-4 was significantly more often detected in the group of patients with a shorter duration of the disease and a progressive course SSD, a skin lesion in the stage of dense edema. The high incidence of scleroderma lung lesion in these patients with significantly shorter duration of SSD emphasizes the severity of the pathological process. Some predominance of the frequency and severity of trophic disorders, telangiectasia, calcification and gastrointestinal tract lesions in patients with low IL-4 in the blood corresponded to a longer duration of the disease in this group. There were no significant differences in the lesion of other internal organs, as well as the dependence of IL-4 content on clinical forms and the initial course of SSD.

In the group of patients with the level of cytokine IL-4>1 Opg/ml average values of such laboratory activity indicators as CEC (297+1 ZED and 200±143Ed, p=0.05) and gamma globulins (24±5.2% and 21 ±3.9%, p=0.03) they were significantly higher. At the same time, the levels of acute-phase proteins: CRP (0.31±0.26 mg% and 0.68±0.8mg%, p=0.06) and fibrinogen (3.22±1.2 g/l and 3.54±0.8g/l, p=0.2), alpha-2 globulins (10±0.9% and 11+ 1.5%, p=0.04) were lower than in the group of patients with IL-4 content in the blood <10pg/ml.

The frequency of ANF, a-Scl-70 and anticentromeric antibodies, as well as the titer of ANF did not differ between the two groups of patients. Serum IL-4 levels were not correlated with ANF titer (g=0.04, p>0.5). To date, it is safe to talk about an immunoregulation defect leading to uncontrolled synthesis of fibrosinducing cytokines as an important factor in the pathophysiology of fibrosis in SSD. We conducted a study of the content of IL-4, one of the main fibrogenic cytokines, in the blood of patients with SSD in comparison with the clinical manifestations of the disease, forms and features of the course. IL-4 in an amount of > 1 Opg/ml was detected in the sera of 30% of patients, which is consistent with the data of other authors on the presence of this cytokine in the blood of 21-38% of patients with SSD. A number of features have been established during the course of the disease

in this group of patients: negative clinical and laboratory dynamics at the time of examination (an increase in skin densification, the appearance or progression of existing visceral pathology, an increase in immunological activity) and the presence of high laboratory activity (CEC, u-globulins). The need to prescribe immunosuppressive therapy in most cases confirms the active course of the fibrous process in these patients. At the same time, the relationship of IL-4 with such clinical manifestations of the disease such as arthritis and polymyositis have not been established. These data, as well as the reverse nature of the relationship of IL-4 with acute-phase reactants, suggest a different genesis of the fibrous and inflammatory musculoskeletal process in scleroderma, currently combined in the concept of SSD activity. The main source of IL-4 blood is circulating T lymphocytes, therefore, the cytokine level may indicate the intensity of T cell

activation, accompanied by the migration of lymphocytes into tissues and the formation of T cell infiltrates in SSD. Therefore, the level of IL-4 in serum may indirectly reflect the severity of local immune processes associated with fibrosis. We consider this as one of the possible explanations for the relationship between the content of IL-4 in the blood and the activity of SSDs. The correlation of IL-4 levels with IL-2, a well-known marker of T-cell activation and progression of SSD, revealed by B.W. Needleman, is a confirmation. Comparison of IL-4 with individual indicators of laboratory activity of SSDs (CEC, gamma globulins, total protein) did not allow to establish a reliable correlation. The latter parameters, which are widely used in determining the activity of SSDs, reflect the humoral immune response and the production of autoantibodies, while the level of IL-4 seems to indicate the state of the T-cell link. The leading importance of T-cell activation in the progression of SSD suggests the advantages of using IL-4 as a marker of the active phase of the disease over the above laboratory parameters, which are mainly non-specific and pathogenetically not so important in the development of scleroderma. The inverse relationship between IL-4 and the values of CRP, fibrinogen and seromucoid remains unclear. Perhaps it is due to the well-known the inhibitory effect of IL-4 on the production of proinflammatory cytokines (IL-1 beta, IL-6, TNF-alpha), inducing the synthesis of acute phase proteins in the liver.

CONCLUSIONS

Thus, IL-4 in SSD can be considered as a marker of the active phase of the fibrous process. Based on an increase in its level in the blood , it is possible to isolate patients with a progressive course of the disease who need the use of immunosuppressive therapy. As a rule, these are patients with early SSD, occurring with high laboratory activity; the main visceral pathology determining the severity of their condition is scleroderma lung lesion.

In the future, clinical studies in dynamics are needed to clarify the possibility of using serum IL-4 levels in monitoring the progression of SSD.

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