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DETERMINATION OF CHANGES IN THE CONTENT OF PRO- AND ANTI-INFLAMMATORY CYTOKINES IN PATIENTS WITH TRUE AND MICROBIAL ECZEMA

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The widespread, long-term chronic course of the disease, the complex nature of the disorders and insufficiently studied pathogenesis determine the interest in the problem of eczema. The purpose of this study was to study the features of changes in the content of peripheral blood interleukins depending on the clinical course, severity and duration of eczema to determine the role of the identified disorders in the development of the inflammatory process. In 40 patients with true and microbial eczema, anamnestic and clinical features, the nature of the disease, as well as the use of highly sensitive ELISA determined the features of cytokine status depending on the selected parameters. These features of cytokine imbalance, which depend on the clinical manifestations of dermatosis, suggest their role in the development of exudative-destructive process in eczema. The concentration of IL-2 in both groups decreased, and IL-4 increased, more pronounced in the 2nd group. The revealed disorders in microbial and true eczema of the level of pro- and anti-inflammatory IL, and the correlation of interleukin parameters have pathogenetic significance and determine the features of the clinical course of this disease.

Key words: true eczema, microbial eczema, immune system, cytokines, pathogenesis of eczema.

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ВИЗНАЧЕННЯ ЗМІН ВМІСТУ ПРО- ТА ПРОТИЗАПАЛЬНИХ ЦИТОКІНІВ У ХВОРИХ НА СПРАВЖНЮ ТА МІКРОБНУ ЕКЗЕМУ

Широке поширення, тривалий хронічний перебіг захворювання, комплексний характер порушень і недостатньо вивчений патогенез зумовлюють інтерес до проблеми екземи. Метою даного дослідження було вивчення особливостей зміни вмісту інтерлейкінів периферичної крові залежно від клінічного перебігу, тяжкості та тривалості екземи для визначення ролі виявлених порушень у розвитку запального процесу. У 40 пацієнтів з істинною та мікробною екземою анамнестичні та клінічні особливості, характер захворювання, а також використання високочутливого ІФА визначали особливості цитокінового статусу залежно від обраних параметрів. Ці особливості дисбалансу цитокінів, які залежать від клінічних проявів дерматозу, свідчать про їх роль у розвитку ексудативно-деструктивного процесу при екземі. Концентрація ІЛ-2 в обох групах знижувалася, ІЛ-4 підвищувалася, більш виражена становила у 2-й групі. Виявлені порушення при мікробній та істинній екземі рівня про- та протизапальної ІЛ, співвідношення показників інтерлейкінів мають патогенетичне значення та визначають особливості клінічного перебігу цього захворювання.

Ключові слова: справжня екзема, мікробна екзема, імунна система, цитокіни, патогенез екземи.

The study is a fragment of the research project, "Optimization of disorders of adaptation mechanisms in acute and chronic dermatoses", state registration No. 0119U002905.

The problem of studying the mechanism of eczema is one of the most relevant in modern dermatology, due to the high level of morbidity, increasing the number of trigger factors, chronic recurrent course, causing psychosocial maladaptation of patients [4, 6, 7].

Numerous studies indicate the complex nature of disorders of many body systems in patients with eczema [3, 8, 10], but the leading role is given to genetically determined or acquired immune disorders [5]. The role of immune mechanisms in the development of dermatosis cannot be fully understood, because the state of the cellular and humoral parts of the immune defense is characterized by multidirectional changes. A special role in the development and course of exudative-destructive inflammation in the disease is played by cytokines, the biological action of which is very diverse. Cytokines are one of the main regulators of intercellular interaction, are actively involved in the implementation of the immune response, inflammatory reactions and others. [2, 9].

The purpose of the study was to determine changes in the concentration of pro- and anti-inflammatory interleukins in the blood of patients with true and microbial eczema, depending on the stage of the disease, as well as the severity and duration of the process.

Materials and methods. The study was performed in the city clinical dermatological and venereological dispensary No. 5 in Kharkiv. Deontological aspects are resolved taking into account the legislation in Ukraine and Model Regulations on the Ethics Commission, as amended, World Health Association Declaration of Helsinki.

There were 40 patients with true and microbial eczema (28 men and 12 women) aged 19 to 64 years. The duration of the disease varied significantly and averaged 4.8±0.4 years.

To characterize the severity of eczema, a scoring system was used (to quantify the severity of the process at the initial examination, in the dynamics of observation of patients, as well as in the subsequent mathematical processing of the data) (Bocharova, 1994).

The average severity was 2.63±0.08 points.

According to the course of dermatosis, patients were distributed as follows: inpatient course was observed in 24 (59 %) patients, progressive slowly progressive course – in 6 (16 %) patients, progressive course with rapid progression – in 10 (24 %) patients. Inpatients of reproductive age were dominated by stationary dermatosis – 14 (36 %) patients, progressive course with slow progression was observed in 2 (5 %) patients, progressive course with rapid progression – in 4 patients (10 %), while in patients older than 45 years there was a tendency to increase the incidence of progressive: slowly progressive – 6 (15 %) patients, rapidly progressing – 6 (15 %) patients, and 10 patients with inpatient eczema accounted for 25 %.

According to the degree of skin lesions, limited forms of dermatosis were observed in 23 (57 %) patients, common – in 17 (42 %) patients. The area of the lesion was distributed as follows: lesions up to 10 % of the total area of the skin – 7 (18 %) patients, from 10 to 30 % – 15 (38 %) patients, from 30 to 50 % – 12 (28 %) patients, from 50 to 75 % – 6 (15 %) patients.

The clinical picture in patients with true eczema was characterized by the presence of 13 (32.5 %) patients with dyshidrotic eczema. In 3 (7.5 %) patients pruriginous eczema was detected. Lichenified eczema presented in 4 (10 %) patients.

Microbial eczema was detected in 20 patients: 10 patients (25.0 %) with varicose eczema and 10 patients (25 %) with paratraumatic eczema were observed. The process in 13 patients was accompanied by itching, in the presence of ulcers (in 4 patients) – a sharp pain. The occurrence of varicose eczema was facilitated by the varicose symptom complex in 8 patients. Paratraumatic eczema arose on the periphery of a trophic ulcer of the tibia in 4 patients, in the area of postoperative cult in one patient, around the fistulous course in two patients, after injury in 12 patients.

Cytokine profile (IL – IL-2, IL-4, IL-6, IL-8, IL-10) was studied in 40 patients with eczema. Enzyme-linked immunosorbent assay was used in the study of interleukins.

Results of the study and their discussion. We studied the content of pro-inflammatory (IL-2, IL-6, IL-8) and anti-inflammatory cytokines (IL-4, IL-10) in patients with true and microbial eczema in exacerbation and remission.

As a result of studies conducted in patients with true and microbial eczema in general (Table 1) found a significant deviation of the content of IL from healthy individuals.

Table 1

The level of IL (M ± δ) in the blood of patients with various forms of eczema in the acute stage

Index, pcg/ml	Patients with various forms of eczema		Control group, n=10
	True, n=20, 1gr	Microbial, n=20, 2gr	
IL-2	22.61±2.81*	19.06±1.23*	13.74±2.36
IL-4	18.65±1.73	25.88±2.31*	12.01±1.79
IL-6	18.78±1.97	26.12±2.93	21.86±1.74
IL-8	28.35±3.52	38.91±3.82*	24.94±1.32
IL-10	25.45±2.59	28.54±2.69	21.64±2.50

Note. The differences are significant between the indicators in patients and individuals in the control group at $p < 0.05$ – *, $p < 0.01$ – **.

The level of IL-2 in patients with true and microbial eczema in the acute stage in the blood serum exceeded ($p<0.05$), similar parameters in the control group. Also, the level of IL-6 significantly exceeded ($p<0.01$) parameters in the control group. However, the level of IL-8 in patients with true and microbial eczema in the serum slightly exceeded ($p <0.05$), the parameters in the control group.

In patients with true and microbial eczema in the acute stage, the content of IL-2, IL-4, IL-6, IL-8, IL-10 in the blood was higher compared to the control group with almost healthy patients.

The dynamics of cytokines in patients with eczema depending on the duration of the process are presented in table 2.

Table 2

The level of IL (M±δ) in the blood of patients with different duration of eczema

Index, pcg/ml		Patients with different duration of eczema, years		Control group, n=10
		before 5, n=20	above 5, n=20	
True eczema	IL-2	20.31±2.31*	25.06±1.13*	13.74±2.36
	IL-4	17.03±1.23	29.18±3.31*	12.01±1.79
	IL-6	16.78±1.87	28.92±2.33	21.86±1.74
	IL-8	30.35±3.82	39.98±3.05*	24.94±1.32
	IL-10	26.95±2.96	30.58±2.89	21.64±2.50
Microbial eczema	IL-2	28.65±3.51*	27.66±1.53*	13.74±2.36
	IL-4	24.15±1.95	30.88±2.38*	12.01±1.79
	IL-6	26.28±2.07	29.92±2.95	21.86±1.74
	IL-8	34.25±3.42	41.01±3.12*	24.94±1.32
	IL-10	29.14±2.49	34.54±2.19	21.64±2.50

Note. The differences are significant between the indicators in patients and individuals in the control group at $p < 0.05$ – *, $p < 0.01$ – **.

In patients suffering from microbial and true eczema for up to 5 years, the level of IL-10 increased in the serum for more than 5 years ($p<0.01$) compared with healthy individuals. The IL-2 content was almost unchanged ($p<0.05$) and was not associated with disease duration.

The concentration of IL-4 in the blood increased with the term of dermatosis for more than 5 years. IL-6 levels increased significantly only in patients over 5 years in the evening. Also, patients increased the content of IL-8 with a disease duration of more than 5 years ($p<0.01$).

Comparison of the average values of cytokines in groups of patients depending on the duration of dermatosis revealed a significant difference between the content of IL-2, IL-4, IL-6, IL-8, and IL-10 with a duration of eczema up to and over 5 years ($p<0.05$).

Thus, the study found significant violations of the cytokine profile of the blood in 84.5 % of patients with true and microbial eczema, which were manifested by an imbalance of pro- and anti-inflammatory IL. Also, in patients with true and microbial eczema, significant differences were found. However, divergent changes have been identified.

An increase in the content of increase in IL-4 in 2.6, decrease in IL-2 in 1.9, normal value of IL-6 compared with similar indicators of the control group.

Normal level of IL-2, IL-4 content and increase in 2.5 years, increase in IL-6 in 2.2 years, increase in IL-8 and IL-10 in 2.3 and 3.1, respectively. In the 2nd group patients found a slight decrease in the content of IL-2 and IL-6, an increase in IL-4 in 3.5 years, IL-8 in 2.6 and IL-10 in 3.7. Comparison of quantitative changes in the cytokine profile in patients revealed a decrease in the level of IL-2 and an increase in IL-4 in patients of the 2nd group. compared with patients in the 1st group.

By acting on T and B cells, proinflammatory ILs are regulators of the immune response. The decrease in the level of IL-2, found in a study (especially in patients of the 2nd group), inducing T cell proliferation, maturation of cytotoxic T lymphocytes, proliferation and differentiation of B lymphocytes, explains the existence of secondary immunodeficiency in eczema, previously established by researchers [1, 12]. IL-2 is secreted primarily by Th-lymphocytes (mainly Th1) and is required for the generation of Th1 and Th2 cells, it potentiates the production of characteristic cytokines that are synthesized by these differentiated cells [3, 11].

Increased levels of anti-inflammatory IL in patients with eczema indicate a predominance of the Th2-immune response in dermatosis, but may also be aimed at the proliferation of T lymphocytes due to a decrease in IL-2, which is secreted mainly by Th1 cells. The mechanisms of activation of the proinflammatory cytokine system probably play a role in the autoimmune processes characteristic of eczema, as well as the imbalance of the oxidative homeostasis system, which usually accompanies the exacerbation of the disease.

Features of cytokine imbalance, depending on the clinical manifestations of dermatosis, which suggests their role in the development of exudative-destructive process in eczema. The concentration of IL-2 in both groups decreased, IL-4 increased, more pronounced in the 2nd group. In the 1st group the value of IL-2 increased ($p<0.05$), whereas in the 2nd group – significantly decreased during the day ($p<0.05–0.01$). The content of IL-4 in the blood of patients with the 1st gr. increased o for the duration of

eczema up to 5 years, more pronounced for the duration of more than 5 years (p<0.01), 2nd group increased regardless of the duration of the disease, more significant for more than 5 years (p<0.05–0.01). At patients of the 1st gr. the level of IL-6 increased in the presence of dermatosis up to 5 years, during the day – with the duration of dermatosis over 5 years, 2nd group, on the contrary, decreased only with the disease up to 5 years (p <0.05).

Correlation analysis revealed a positive relationship between anti-inflammatory and inflammatory cytokine levels (in the 1st group r=0.79, (p<0.01); in the 2nd group r=0.56, (p<0.01) and the clinical form of the disease (in the 1st group r=0.61, p<0.01, in the 2nd group r=0.79, p<0.01), duration (in the 1st group r = 0.68, p<0.01; in 2nd group r=0.51, p <0.01), IL-4 and duration (in the 1st group r=0.49, p <0.05; in the 2nd group r=0.76, p <0.01).

Conclusion

The revealed disorders in microbial and true eczema of the cytokine profile of blood with significant changes in the level of pro- and anti-inflammatory IL, decrease in the content of the main T-cell factor regulating IL-2, correlation of interleukin parameters with clinical forms of dermatosis and duration of the process. pathogenesis of this disease. The peculiarities of cytokine imbalance, which depend on the clinical manifestations of dermatosis, have been established, which suggests their role in the development of the exudative-destructive process in eczema. Violations of the cytokine profile of blood with eczema with significant changes in the level of pro- and anti-inflammatory IL, decreased content of the main T-cell factor regulating IL-2, correlation of interleukin and hormonal parameters require involvement in complex therapy of drugs that normalize immune regulation. Features of cytokine imbalance, depending on the clinical manifestations of dermatosis, as well as a close correlation have been established.

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