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INTERLEUKIN-17A AND INTERLEUKIN-18 LEVEL IN THE BLOOD SERUM OF PATIENTS WITH DIFFERENT CLINICAL COURSE OF ROSACEA

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Abstract

Introduction. Rosacea is a common chronic dermatosis characterized by lesions of open areas of the skin (face) and torpidity to treatment.
The objective of our study was to determine and analyze the content of proinflammatory cytokines – interleukin-17A (IL-17A) and interleukin-18 (IL-18) in the serum of patients with rosacea, depending on the nature of the clinical course of dermatosis.
Material and methods. The study involved 36 patients with rosacea, 17 of them diagnosed with erythema-telangiectatic form and 19 with papulo-pustular form of rosacea. In 18 patients, the dermatosis lasted for up to 6 months, in the remaining 18 patients for more than 6 months. In patients with rosacea, the serum content of individual cytokines, interleukin-17A and interleukin-18 was determined by the immunoassay assay.
Results. It has been established that the content of proinflammatory cytokines in the serum of patients with rosacea is reliably elevated compared to that in the control group – IL-17A (4.11 times, $p < 0.001$) and IL-18 (1.63 times, $p = 0.002$). A more significant increase in the level of IL-17A in the blood serum of patients with the papulo-pustular form of rosacea

Résumé

Le niveau d'interleukine-17A et d'interleukine-18 dans le sérum des patients avec l'évolution clinique différente de la rosacée

Introduction. La rosacée est une dermatose chronique commune se manifestant par les lésions cutanées des zones ouvertes (visage) et au caractère torpide du traitement, ce qui détermine la pertinence de l'étude de ses facteurs pathogénétiques et l'amélioration du traitement de cette dermatose.
Le but de cette étude est de déterminer et d'analyser le contenu des cytokines pro-inflammatoires – l'interleukine-17A et l'interleukine-18 – dans le sérum des patients atteints de rosacée en fonction de la nature de l'évolution clinique de la dermatose.
Méthodes. L'examen des 36 patients atteints de rosacée, dont les 17 ont une forme érythémateuse-télangiectasique et les 19 sont au stade papulo-pustulaire de rosacée. Chez les 18 patients, la durée de la dermatose est moins de 6 mois et, chez les autres 18, la maladie dure plus de 6 mois. On a fait le test d'immunodosage du sérum afin de révéler la teneur en cytokines – l'interleukine-17A et l'interleukine-18 (IL-17A, IL-18).

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compared to the erythema-telangiectatic form and duration of dermatosis for more than six months has been found. At the same time, the level of IL-18 tended to increase more significantly in the early stages of dermatosis – in patients with erythema-telangiectatic stage of rosacea and duration of the disease up to 6 months, with subsequent decrease in the level of IL-18 in patients with papulo-pustular stage and duration of dermatosis more than 6 months.

Conclusions. The patients with rosacea were found to have an elevated level of proinflammatory cytokines – interleukin-17A and interleukin-18. The changes in the cytokines depended on the nature of clinical course of rosacea, indicating a significant role in the regulation of inflammatory processes in the pathogenesis of dermatosis and the importance of monitoring the content of blood serum IL-17A and IL-18, as prognostic criteria for clinical course and effective treatment of rosacea.

Keywords: rosacea, clinical course, interleukin-17A, interleukin-18.

Abbreviations: IL – Interleukin; TNF-α – Tumor Necrosis Factor-α; INF-γ – Interferon-γ; VEGF – Vascular Endothelial Growth Factor.

Résultats. On a établi que dans le sérum de patients atteints de rosacée le contenu de la cytologie inflammatoire est considérablement augmenté par rapport à celui du groupe de contrôle: IL-17A (à 4,11 fois, p <0,001) et l'IL-18 (à 1,63 fois, p=0,002). On a constaté une augmentation significative du niveau d'IL-17A dans le sérum des patients à la rosacée papulo-pustuleuse par rapport aux patients à la rosacée érythémateuse-télangiectasique avec la durée de plus de six mois, parallèlement on a révélé la tendance à une augmentation significative du niveau d'IL-18 aux premiers stades de la dermatose chez les patients à la rosacée érythémateuse-télangiectasique avec la durée de la maladie ne dépassant pas 6 mois, suivi de la diminution du niveau de l'IL-18 chez les patients à la rosacée papulo-pustuleuse avec la durée de plus de 6 mois.

Conclusions. On a établi chez les patients atteints de rosacée un taux élevé de cytokines pro-inflammatoires – interleukine-17A et interleukine-18, la dépendance des changements des cytokines étudiées de l'évolution clinique de la rosacée ce qui révèle la valeur significative des cytokines dans la régulation des processus inflammatoires de la pathogenèse de la dermatose et signale l'importance de surveiller le contenu de IL-17A et IL-18 dans le sérum du sang comme critères pronostiques pour l'évolution clinique et l'efficacité du traitement de la rosacée.

Mots-clés: rosacée, évolution clinique, interleukine-17A, interleukine-18.

Abréviations: IL – Interleukine; TNF-α – Facteur de nécrose tumorale; INF-γ – interféron-γ; VEGF – Facteur de croissance de l'endothélium vasculaire.

Introduction

Rosacea (pink acne) has been one of the most urgent problems of dermatology in recent years due to the prevalence of dermatosis, as well as to its clinical features. Rosacea is a chronic inflammatory disease of the skin, which affects about 3% of the world's population. Patients with rosacea represent 5% to 12% of dermatological patients[1,2].

The dermatosis most frequently develops in women of active working age (30-50 years). The rash is mainly localized on the skin of the central part of the face (forehead, cheeks, chin). The dermatosis tends to last long, the patients developing resistance to the drugs used for treatment, which in general has a negative impact on the psycho-emotional state of patients, reducing their ability to work and social activity[3-5]. This highlights the medical and social importance of the problem of rosacea and the relevance of scientific research aimed at identifying the pathogenetic factors and improving the comprehensive treatment of patients with rosacea[1,6,7].

Rosacea is a multifactorial dermatosis, the development of which is due to the complex action of exogenous factors (insolation, temperature and chemical stimuli, eating spicy food, etc.), excessive reproduction of *Demodex folliculorum* mites in the skin, as well as endogenous mechanisms (neurovegetative dysfunctions, constitutional angiopathies, disorders in the endocrine regulation, diseases of the digestive system, chronic foci of infection, etc.)[3,8-10].

A significant role in the development and course of rosacea belongs to an impairment of the immunological reactivity of the patient[1,3,6]. The study of cytokines' role in the regulation of pathological processes in chronic dermatoses, particularly rosacea, by determining the nature of changes in the serum content of interleukins, is relevant[11-16]. Interleukins are secretory

proteins of the immune system that ensure the interaction of immunocompetent cells among themselves and the connection of the immune system with other systems of the body, regulate the proliferation of fibroblasts, endothelial cells, stimulate the recovery of the epithelial layer, the development and outcome of inflammatory processes in the skin[15-18].

However, there are only a few studies about the cytokine profile in patients with rosacea, and they often only indicate the general trends of disorders of the studied parameters, without an analysis of their changes in patients with different clinical course of dermatosis. For instance, there are reports of an elevated level of proinflammatory cytokines – tumor necrosis factor-α (TNF-α), interleukin-1β and interleukin-6 – in the blood serum of patients with rosacea[11,15]. Other reports contain evidence of an elevated serum content of interleukin-8, interleukin-10 and interleukin-12, interleukin-17 and interleukin-18, but without differentiating the changes depending on the clinical stage of dermatosis[7,12,13,15,16].

The objective of the study was to determine and analyze the content of proinflammatory cytokines – interleukin-17A and interleukin-18 in the serum of patients with rosacea, depending on the nature of the clinical course of dermatosis.

Material and methods

The study involved 36 patients with rosacea, including 25 women and 11 men, aged 26 to 67 years, who were examined and treated between 2016 and 2018 in the Regional Dermatovenerological Hospital of Chernivtsi, Ukraine. All patients signed an informed consent to participate in the study. In all the patients included in the study, clinical and laboratory examinations have been performed. The patients with papulo-pustular stage of rosacea were hospitalized in the Regional Dermatovenerological Hospital, and the patients with erythema- telangiectatic form were treated ambulatory. All patients were treated by the same dermatologist.

The following criteria were used to include patients in the study: clinical manifestations of rosacea on the skin, the patients' consent to participate in the study, the absence of infectious and somatic diseases at the time of examination, the absence of harmful habits, etc. The criteria for exclusion from the study were: the lack of consent of the patient to participate in the study, the presence of diagnosed demodicosis, the presence of infectious and/ or associated somatic diseases or their exacerbations in patients at the time of examination, the presence of harmful habits in the patient.

According to clinical criteria[2,3], 17 patients (47.2%) were diagnosed with erythema- telangiectatic form of rosacea, 19 of them (52.8%) were in papulo-pustular stage of dermatosis. In 18 patients (50.0%), the dermatosis lasted for up to 6 months, in the remaining 18 patients (50.0%) – for more than 6 months.

The content of proinflammatory cytokines – interleukin-17A (IL-17A), which makes up the highest proportion and is the most active among other cytokines of the family of IL-17, as well as the level of interleukin-18 (IL-18), were determined in the patients' blood serum; the research was carried out by the method of immunoassay analysis, according to common methods, using licensed diagnostic test systems.

The control group consisted of 18 practically healthy individuals (donors) of the same age and sex.

Statistical processing of the results of the research was carried out by statistical analysis methods on a personal computer, using the packages of licensed Microsoft Excel and STATISTICA 6.0 StatSoft Inc. The mean values of the indicators (M) and their standard error (m) were determined. To assess the likelihood of the difference between the indicators, Student's t-criterion was used, the difference being considered significant when $p < 0.05$.

Results

The content of proinflammatory cytokines in the serum of patients with rosacea was significantly elevated: IL-17A by 4.11 times ($p < 0.001$) and IL-18 by 1.63 times ($p = 0.002$), compared to that in the individuals from the control group, which are presented in Table 1.

The analysis of the studied cytokines in the blood serum of patients with different clinical stages (forms) of rosacea showed that the level of IL-17A is significantly higher in patients with the papulo-pustular stage (form) of rosacea as compared to the same indicator in the control group – by 4.97 times (17.68

Table 1. Indices of IL-17A and IL-18 content in the blood serum of patients suffering from rosacea (M±m)

Values, measurement units	*Patients with rosacea, n=36*	*Control group, n=18*	*p*
Interleukin-17A, pg/mL	14.76 ± 1.49	3.56 ± 0.75	p <0.001
Interleukin-18, pg/mL	166.94 ± 13.91	102.25 ± 5.74	p =0.002

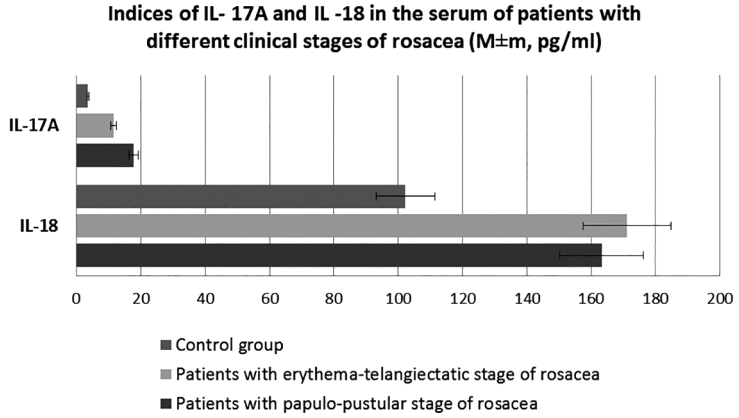

Figure. 1. Indices of IL –17A and IL –18 in the serum of patients with different clinical stages of rosacea (M±m, pg/ml).

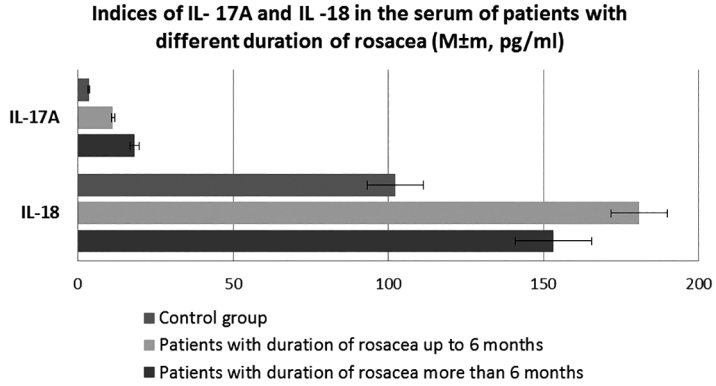

Figure. 2. Indices of IL –17A and IL –18 in the serum of patients with different duration of rosacea (M±m, pg/ml).

± 1.78 pg/mL, in control group subjects – 3.56 ± 0.75 pg/mL; p <0.001) and in comparison with the index of IL-17A in patients with erythema-telangiectatic stage of dermatosis – by 1.54 times (11.49 ± 2.23 pg/mL; p = 0.035) (Figure 1).

At the same time, patients with the initial erythema-telangiectatic form of rosacea were found to have the level of IL-18 elevated more significantly – by 1.63 times (171.12 ± 20.40 pg/mL) as compared to the control group (102.25 ± 5.74 pg/mL; p = 0.002) than the patients with the papulo-pustular stage (form) rosacea – by 1.59 times (163.21±19.49 pg/mL; p = 0.006 respectively) (Figure 1).

The comparative analysis of the cytokine level in the blood serum of patients with rosacea and different duration of dermatosis showed that the level of IL-17A is significantly higher in patients with rosacea and the duration of dermatosis for more than six months as compared to that in the control group – by 5.12 times (18.22±1.79 pg/mL, in the control group 3.56 ± 0.75 pg/ml; p <0.001) and in comparison with the serum IL-17A level in patients with short evolution of dermatosis (up to 6 months) – by 1.61 times (11.29±2.12 pg/mL, p = 0.016) (Figure 2).

There was a tendency to a more significant increase in the level of IL-18 (180.72±19.81 pg/mL) in patients with early stages of rosacea with a duration of dermatosis up to 6 months – by 1.77 times as compared to the control group (102.25 ± 5.74 pg/mL; p <0.001) compared to patients with a longer duration of rosacea (for more than six months) – by 1.49 times (153.17±19.54 pg/mL, p = 0.017 respectively) (Figure 2).

Discussion

In patients with rosacea, the content of IL-17A in the blood serum was significantly elevated. This interleukin belongs to proinflammatory cytokines, it is produced by activated CD4 + (T-helper type 1 and type 2) and CD8 + T-cells, connects the immune and hematopoietic systems, activates angiogenesis through VEGF, enhances the effect of many proinflammatory cytokines such as TNF-α, INF-γ, IL-1, IL-6 and IL-8, which can enhance inflammation in

the skin, including purulent-inflammatory processes[15,17]. An elevated level of IL-17A may be one of the most important pathogenetic factors in the development of erythema-telangiectatic stage of rosacea, chronicization of dermatoses and development of purulent-inflammatory processes in the skin of patients with rosacea, as evidenced by a more significant increase in the content of IL-17A in the blood serum of patients with the papulo-pustular stage of rosacea and the duration of dermatosis for more than six months.

The patients with rosacea had a significant increase in the content of IL-18 in the blood serum. IL-18 is synthesized by keratinocytes, macrophages, monocytes, Langerhans cells and is an important modulator of the immune response, playing an important role in the T-helper response of type 1, which can stimulate the production of INF-γ in T-lymphocytes and NK-cells. It has also antiinfectious and antitumor effects, playing an important role in the pathogenesis of inflammatory processes in the skin[12,17,19].

A higher increase in the level of IL-18 in patients with initial erythema- telangiectatic stage of rosacea and duration of the disease up to 6 months revealed in the patients with rosacea indicates the role of IL-18 in the inflammatory processes in the early stages of rosacea. The gradual decrease in the level of IL-18 in the serum of patients with rosacea, due to the reduction of anti-infectious and antitumor control, can contribute to the development of infiltrative and purulent-inflammatory processes in the skin, which, in general, should be taken into account for the diagnostic and therapeutic procedures in such patients.

Conclusions

The patients with rosacea have a significantly elevated level of proinflammatory cytokines in the serum – interleukin-17A (4.11 times, p <0.001) and interleukin-18 (1.63 times, p=0.002) compared to individuals from the control group.

A more significant increase in the level of IL-17A in the blood serum of patients with papulo-pustular stage of rosacea and duration of dermatosis for more than six months has been found, compared to the erythema-telangiectatic stage. The level of IL-18 tended to increase more significantly in the early stages of dermatosis – in patients with erythema – telangiectatic stage of rosacea and duration of the disease up to 6 months, with subsequent decrease in the level of IL-18 in patients with papulo-pustular stage and duration of dermatosis more than 6 months.

The changes in proinflammatory cytokines (IL-17A, IL-18) depend on the nature of the clinical course of rosacea, indicating a significant role of cytokines in the regulation of inflammatory processes in the pathogenesis of dermatosis and the importance of monitoring the content of serum IL-17A and IL-18, as prognostic criteria for clinical course and effective treatment of rosacea.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article"

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study"

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