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DISORDERS OF INNATE IMMUNITY IN VARIOUS FORMS OF THE CHRONIC ECZEMA

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The role of adaptive immunity in the mechanism of development of eczema as a chronic relapsing dermatosis is proven. The infectious nature of the process in microbial eczema, dysbiosis of skin microbiota and frequent bacterial complications in idiopathic (genuine) eczema primarily indicate disorders of innate immunity. The purpose of the study was to determine the cellular and humoral links of innate immunity in patients with various clinical forms of chronic eczema. Suppression of phagocytic activity of neutrophils in patients with microbial eczema due to weakening the absorbing and digesting ability (decrease in the value of the phagocytic index, phagocytic number and index of completion of phagocytosis) was established, while in patients with idiopathic eczema only the index of completion of phagocytosis was reliably reduced. For the first time, a decreased level of the antimicrobial protein lactoferrin was determined in both forms of dermatosis compared to that in individuals of the control group. The level of the antimicrobial peptide β -defensin 2 increased in all patients relative to that in the control group, more significantly in idiopathic eczema.

Key words: idiopathic eczema, microbial eczema, pathogenesis, innate immunity, phagocytic activity of neutrophils, lactoferrin, β -defensin 2.

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РОЗЛАДИ ВРОДЖЕНОГО ІМУНІТЕТУ ПРИ РІЗНИХ ФОРМАХ ХРОНІЧНОЇ ЕКЗЕМИ

Роль адаптивного імунітету у механізмі розвитку екземи як хронічного рецидивуючого дерматозу є доведеною. Інфекційний характер процесу при мікробній екземі, порушення мікробіоти шкіри і часті бактеріальні ускладнення при істинній екземі свідчать в першу чергу про розлади вродженого імунітету. Метою роботи було вивчення клітинного і гуморального компонентів вродженого імунітету у пацієнтів з різними клінічними формами хронічної екземи. Встановлено, що у пацієнтів з мікробною екземою пригнічення фагоцитарної активності нейтрофілів відбувається шляхом ослаблення поглинальної та перетравлюючої здібності (пониження значення фагоцитарного індексу, фагоцитарного числа та індексу завершеності фагоцитозу), при цьому у хворих на істинну екзему достовірно зменшувався тільки індекс завершеності фагоцитозу. Вперше визначено пониження рівня антимікробного білка лактоферину при обох формах дерматозу порівняно з таким у осіб контрольної групи. Вміст антимікробного пептиду β -дефензину 2 збільшувався в усіх пацієнтів відносно такого у контрольній групі, більш значимо при істинній екземі.

Ключові слова: істинна екзема, мікробна екзема, патогенез, вроджений імунітет, фагоцитарна активність нейтрофілів, лактоферин, β -дефензин 2.

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Eczema is a common multifactorial skin disease characterized by the appearance of polymorphic rashes, an acute inflammatory reaction due to serous inflammation of the skin, itching and recurrences. The formation of a pathological skin process occurs under the influence of endogenous and exogenous factors with the involvement of various organs and regulatory systems in the multi-link mechanism of development – the central and autonomic nervous system, the gastrointestinal tract, the endocrine system and others [6, 8, 15].

The role of immune mechanisms in the development of dermatosis is central, but it cannot be considered fully studied, the state of cellular and humoral links of immune protection is characterized by multidirectional changes [2]. A decisive role in microbial eczema (ME) belongs to bacterial sensitization with representatives of the staphylococci (*S. aureus*, *S. epidermidis*) and β -hemolytic streptococcus playing a leading role, and their association is more often determined. The number of yeast-like fungi of the genus *Candida*, as well as opportunistic microorganisms and gram-negative rods, increases in the lesions [3, 10]. The infectious nature of the process in ME, disruption of the skin microbiota and frequent bacterial complications in idiopathic eczema (IE) indicate a violation of the immune system, primarily innate immunity.

Pattern recognition receptors, the complement system, phagocytosis, NK cells, interferons, endogenous antimicrobial proteins (AMPr) and antimicrobial peptides (AMP) play the most important role in the body's innate defense mechanisms [1, 9]. Phagocytosis belongs to innate, conservative and permanent immune processes in the human body. The potential of the protective functions of the body largely depends on the degree of activity of neutrophil granulocytes, namely the content of biologically active compounds in the granules and

their adequate response to external influences – an increase in phagocytic and antimicrobial activity, the release (secretion) of granular contents into the extracellular environment, the generation of reactive oxygen species and others. A marker of specific granules of neutrophils is iron-binding AMPrlactoferrin (Lf). The role of human AMP β -defensins (hBD 1-4), which are produced mainly by the epithelium of the skin and mucous membranes of the respiratory, intestinal or genitourinary tracts, as well as by peripheral blood cells, has been sufficiently studied [13]. Defensins are modulators of inflammation and activators of the adaptive immune response – they directly stimulate the migration of immune cells, promote the release of pro-inflammatory cytokines and activate antigen-presenting cells in the direction of the Th1 immune response.

Research conducted in recent years in patients with eczema is mainly devoted to the study of adaptive immunity [2, 8]. Today, there is an assumption that innate immunity is a trigger of inflammatory processes of barrier tissues –skin and mucous membranes [7]. Individual researchers pointed out the importance of violations of non-specific protection of the body, namely inhibition of phagocytosis, increased expression of Toll-like receptors (TLR)2, TLR4 as a possible mechanism for the development and progression of ME [4, 5]. The state of cellular and humoral factors of innate immunity in patients with various clinical forms of chronic eczema (ChrE) has not been studied in depth. Unresolved problems indicate the expediency of further study of the pathogenetic mechanisms of dermatosis, which will contribute to increasing the effectiveness of therapy and improving the quality of life of patients.

The purpose of the study was to evaluate the phagocytic activity of neutrophils, and the level of Lf, hBD-2 in the blood serum of patients with chronic idiopathic and microbial eczema, to conduct a comparative analysis of laboratory parameters.

Materials and methods. Study was carried out during the examination of 48 patients (20 men and 28 women) aged 28–54 years with ChrE who came to the clinic with an exacerbation of the disease. Criteria for patient inclusion in the study: the presence of IE and ME, age over 18 years, duration of dermatosis 6 months and more, no treatment with systemic or topical corticosteroids during the last 6 months. Criteria for excluding a patient from the study: the presence of hyperkeratotic IE or mycotic ME, complications of secondary IE infection, and concomitant diseases in the acute stage.

Based on the anamnesis and clinical manifestations, the diagnosis of IE (pruriginous, dyshidrotic) was established in 23 patients, ME (nummular, peritraumatic, varicose) – in 25 patients. The average age of patients with IE and MI was 33.7 ± 2.2 years and 36.3 ± 2.5 years, respectively. With IE, women predominated (65.2 %), among patients with ME – men (67.8 %). The duration of dermatosis was from 8 months up to 7 years. Relapses of ChrE in patients were observed from one to four times a year. The severity of eczema (mild, moderate, severe) was assessed according to the Eczema Area Severity Index (EASI) generally accepted in dermatological practice [11]. Patients with IE and ME did not differ among themselves in terms of age, the severity of the course, and frequency of disease recurrences.

All patients underwent a traditional general clinical (clinical blood, urine, biochemical blood) and immunological examination. All respondents were informed and signed an agreement to participate in the study. To compare laboratory parameters, 23 practically healthy individuals (10 men and 13 women) aged 25–54 years (average 31.5 ± 2.3 years) were examined as a control group.

The phagocytic activity of polymorphonuclear neutrophils in 48 patients with ChrE was evaluated by the phagocytic index (PhI) – the number of cells capable of interacting with microorganisms, the phagocytic number (PhN) – the average number of microbial bodies per active neutrophil and the index of phagocytosis completion (IPhC), which was calculated from the ratio of the PhN value at different incubation times (after 30 and 120 min).

Quantitative determination of the level of Lf and hBD-2 in the blood serum of 48 patients was carried out by the enzyme immunoassay method on the Labline–90 analyzer (Austria) using appropriate commercial test systems manufactured by Vector-Best JSC (Lactoferrin–IFA–BEST, Novosibirsk) and the company “Elabscience” (Human DEF β 2/DEFB2 ELISA kit, USA) according to the instructions attached to the kits.

Taken blood sampling for laboratory testing has been performed due to a standard technique: peripheral blood obtained by puncture of the ulnar vein has been incubated for 30–40 minutes at room temperature after which the blood serum has been separated. The allotted serum samples have been frozen and stored in Eppendorf-type plastic tubes until testing at a temperature of -20°C before analysis, for no more than 6 months.

Sensitivity of determination during measurement has been estimated at the minimum reliably determined concentration calculated on the basis of the arithmetic mean of ten measurements of the optical density of the calibration sample from the test system. AMP values in both standard calibration dilutions and in test samples have been well reproducible.

Mathematical processing of the results has been carried out by methods of variation statistics in the statistical analysis system STATISTICA 10 (STATISTICA USA software package, Version 10 for Windows 8). In all samples, the nature of distribution to normality has been determined by the criteria of Kolmogorov–Smirnov, and Shapiro–Wilkie. The Mann–Whitney method has been used in the distribution of indicators other than normal. Their arithmetic mean values (M) and their standard errors (m) have been determined to characterize the group of homogeneous units. In order to compare the data between the groups obtained during the study, methods have been used to assess the differences between two independent samples – the Student’s t-criterion and Fisher’s exact method. Differences were considered significant at values of $p < 0.05$.

Results of the study and their discussion. Factors of innate immunity – mechanical barriers (skin, mucous membranes), humoral (AMPr and AMP, complement system, cytokines) and cellular (phagocytosis, contact cytolysis implemented by NK cells and others) provide the first line of defence against ways of introduction of the alien agent. An important role in the initiation of immune processes is played by neutrophils, which first enter the center of inflammation, implement phagocytosis, are capable of producing biocidal radicals, AMPs and enzymes, form neutrophil extracellular traps and participate in the regulation of the formation of skin microbiota.

The number of leukocytes in patients with IE ranged from 5.1 to $7.3 \times 10^9/l$, rod-shaped neutrophils – 1.5–5.0 %, segmentonuclear neutrophils – 52–68 %, ESR – 3–19 mm/h and did not differ from the norm. In 18 out of 25 (72.0 %) patients with ME, leukocytosis over $10 \times 10^9/l$, an increase in rod-shaped neutrophils (7–9 %) with the number of segmented neutrophils (45–64 %), acceleration of ESR (18–25 mm/h) compared to the parameters of healthy individuals. An increase in the number of eosinophils (6–8 %) was determined in 9 (22.5 %) patients with ME.

The study of the phagocytic activity of peripheral blood neutrophil granulocytes in patients with ChrE as a whole revealed a decrease in PhI (51.65 ± 2.11 %), PhN (2.42 ± 0.16 c. u.) and IPhC (0.70 ± 0.05 c. u.), but significantly differed from the similar indicators of the control group values of PhI and IPhC (respectively $p = 0.045$ and $p = 0.041$). The level of Lf in patients with ChrE varied widely – from 214 to 705 ng/ml, on average it was 388.65 ± 19.24 ng/ml and was different from the average statistical value calculated in the control group ($p = 0.040$). The level of hBD-2 in the blood serum of all patients ranged from 730 to 3010 pg/ml. On average it was 1487.25 ± 99.18 pg/ml and significantly exceeded the indicator in practically healthy individuals ($p = 0.047$).

The results of determination of some indicators of the innate immune system of patients with ChrE, depending on the form, are shown in table 1.

Table 1

Indices immunity in patients with various clinical forms of chronic eczema (M±m)

Index	Patients with chronic eczema, n=48		Control group, n=23
	idiopathic, n=23	microbial, n=25	
PhI, %	58.63 ± 2.09	$39.61 \pm 1.57^*$	62.33 ± 2.41
PhN, c. u.	3.02 ± 0.16	$2.17 \pm 0.11^{**}$	3.81 ± 0.22
IPhC, c. u.	$0.80 \pm 0.04^*$	$0.54 \pm 0.03^*$	1.08 ± 0.06
Lf, ng/ml	$492.55 \pm 24.62^*$	$293.44 \pm 12.21^{**}$	655.55 ± 13.71
hBD-2, pg/ml	$2016.40 \pm 109.53^{**}$	$912.09 \pm 30.83^*$	168.45 ± 13.08

Notes: * – significant differences compared with the control group $p < 0.05$; ** – significant differences compared with the control group $p < 0.01$.

The study of the functional activity of phagocytes depending on the clinical forms of dermatosis revealed some features. In most patients with ME, 1.6 times decrease in PhI (39.61 ± 1.57 % vs. 62.33 ± 2.41 % in healthy subjects, $p = 0.043$), by 1.8 times decrease in PhN (2.17 ± 0.11 vs. 3.81 ± 0.25 in healthy subjects, $p = 0.006$) and IPhC 2.0 times (0.54 ± 0.03 vs. 1.08 ± 0.06 in healthy subjects, $p = 0.039$). In patients with IE, a significant decrease by 1.4 times only IPhC (0.80 ± 0.04 c. u., $p = 0.049$) and a tendency to decrease the value of PhN (3.02 ± 0.17 c. u., $p = 0.063$) compared to indices in the control group. A comparison of indices of the functional activity of neutrophils in patients with different forms of ChrE revealed a significant decrease in the ability of cells to absorb and digest objects of phagocytosis in patients with ME than with IE.

The potential of the protective functions of the body largely depends on the degree of activity of neutrophil granulocytes, namely, the content of biologically active compounds in their granules and adequate response to external influences. The level of Lf in patients with IE varied from 312 to 705 ng/ml, with ME – within 214–427 ng/ml. It was established that the level of Lf was reduced in IE by 1.3 times (492.55 ± 24.62 ng/ml), ME by 2.2 times (293.44 ± 12.21 ng/ml) against 655.55 ± 13.71 ng/ml in individuals of the control group (respectively $p = 0.047$ and $p = 0.008$) (fig. 1).

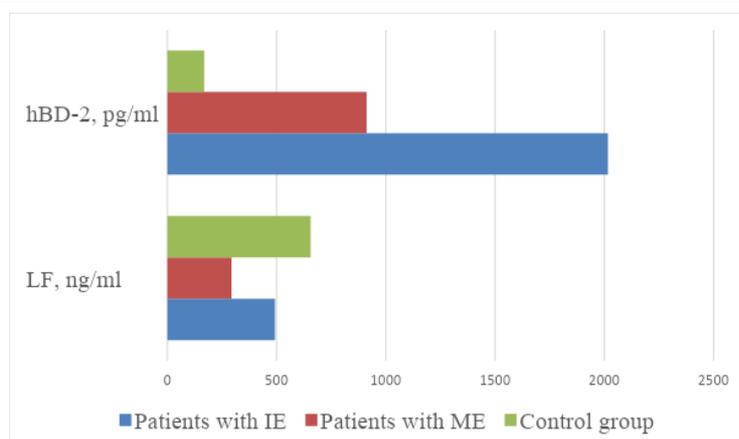


Fig. 1. The level of Lf and hBD-2 in the blood serum of patients with IE and ME

Attention is drawn to the slight fluctuations level of hBD-2 in patients with ME (from 730 to 1170 pg/ml) compared to deviations in patients with IE (from 964 to 3010 pg/ml). In IE, a significant increase (by 12.0 times) in the level of AMP in blood serum was established (2016.40 ± 109.53 pg/ml vs. 168.45 ± 13.08 pg/ml in healthy subjects, $p=0.005$), while in ME level of hBD-2 increased by 5.4 times (912.09 ± 30.83 pg/ml) relative to the value in the control group ($p=0.042$) (fig. 1). A comparison of APM level in both forms of ChrE revealed that the value of hBD-2 in IE was by 2.2 times higher than that in patients with ME.

A significant correlation was found between the level of hBD-2 and the number of blood neutrophils in IE and ME ($r=0.67$, $p=0.049$ and $r=0.42$, $p=0.044$, respectively). The correlation between the level of Lf and the number of neutrophils in the peripheral blood in patients with ChrE has not been determined.

The performed studies allowed us to detect violations of both cellular (phagocytosis) and humoral (AMPr and AMP) components of innate (non-specific) immunity in patients with ChrE. In patients with ME, the functional activity of granulocytes (absorbing and digesting capacity) is reduced, which is confirmed by a decrease in the value of Phi by 36.5 %, PhN by 43.1 % and IPhC by 47.6 %. The data obtained in ME coincide with the results of other researchers [4]. In IE, attention is drawn to a 25.9 % decrease in IPhC, which indicates the insufficiency of the endocytosis process of bacterial antigens in both forms of dermatosis. In incomplete phagocytosis, microorganisms are not digested inside the phagocyte. At the same time, phagocytosed microorganisms survive and can remain in secondary lysosomes for a long time. Failure of all stages of oxygen-independent phagocytosis (chemotaxis, adhesion, endocytosis of antigens) indicates a defect in lysosomal enzymes caused by genetic defects. In both forms of dermatosis, changes in the secretory activity of neutrophils, as well as epidermal cells to the synthesis of AMPr and AMP, were determined.

The activation of neutrophils during the inflammatory process is naturally accompanied by an increase in the secretion of Lf in tissues and its entry into the blood, however, in patients with ChrE, a decrease in the serum level of Lf was found, which was especially significant in patients with ME (by 55.2 %). Lf is considered as a classic multifunctional protein. Lf is a metal-chelating protein, a marker of secondary (specific) granules of neutrophils, which has antibacterial and antiviral activity and a complex of anti-inflammatory properties. The immunomodulatory and anti-inflammatory activity of Lf is associated with the ability to interact with specific cell surface receptors on epithelial cells and cells of the immune system, as well as bind to pathogen-associated molecular patterns, mainly recognized by TLRs. Lf also plays a role in the differentiation, maturation, activation, migration, proliferation, and function of cells belonging to antigen-presenting cells such as B cells, neutrophils, monocytes/macrophages, and dendritic cells [14].

Presumably, the release of Lf in IE as a result of inflammation counteracts skin infection, while in ME it is insufficient to eliminate infectious agents. This implies the presence of a deficiency of Lf accumulation in neutrophils and keratinocytes of patients, which leads to the impossibility of limiting the intensity of the inflammatory process, which may contribute to the spread of eczema. It has been established that a decrease in Lf synthesis can cause a tendency to the formation of biofilms, and this is especially important in ME with frequent relapses [9].

Defensins are the main family of human protective peptides with broad antimicrobial activity and multifaceted immunomodulatory functions. Defensins have an antibacterial effect by binding to the outer shell of bacteria and forming micropores in it, which ultimately disrupts its integrity and leads to the death of the microorganism. The increase in the level of hBD-2, more than 2 times in IE than in ME, indicates the endogenous local release of AMPs and probably plays a role in protecting the skin from infections. The production of defensins can be triggered by commensal bacteria, for example, *S. epidermidis*, with direct antimicrobial activity against staphylococci (including *S. aureus*) and indirect action – activation of TLR2 on keratinocytes.

A significant decrease in the level of AMPr was established in both forms of dermatosis, however, the secretory activity of neutrophils according to the level of Lf decreased more significantly (by 1.7 times) in ME compared to that in IE.

AMP defensins can be produced by both blood neutrophils and keratinocytes and skin immune cells constitutively or in response to danger, such as infection, trauma, or chronic inflammation. Defensins neutralize gram-negative and gram-positive bacteria, acid-resistant rods, fungi, and viruses.

It has now been established that AMPs have not only antimicrobial activity, but also modulate the immune-mediated inflammatory response – they act as chemotactic agents, angiogenic factors, and regulators of cell proliferation and differentiation. Dysregulation of AMPs may contribute to the disease phenotype and affect T-cell-mediated responses and epidermal processes [12].

We believe that the increase in these antimicrobial molecules may reflect the intensity of the body's reaction to damaging factors (infection, trauma, or chronic inflammation). Defensins appear to be more closely associated with neutrophil and epithelial cell activation than Lf in ChrE patients. hBD-2 is an inducible product and belongs to the local system of protection of the epithelium (skin) during inflammation. According to research, in atopic dermatitis, the production of AMP by keratinocytes is disturbed, which may underlie the persistence of microorganisms, in particular, *S. aureus*, *Candida* spp., *Malassezia* spp. on the skin of patients. Perhaps hBD-2 is a potentially important player in the pathogenesis of ChrE, given the disruption of the epidermal barrier, skin microbiota.

Conclusions

1. Phagocytic dysfunction in patients with ME is manifested by a decrease in the PhI by 1.6 times, the PhN by 1.8 times, and the IPhC by 2.0 times compared to the indices in healthy individuals ($p < 0.05$). In patients with IE, a significant decrease of only IPhC was determined by 1.4 times relative to the value in the control group ($p < 0.05$).

2. A decrease in the level of Lf in the blood serum was established in both forms of ChrE – in IE by 1.3 times (492.55 ± 24.62 ng/ml), ME by 2.2 times (293.44 ± 12.21 ng/ml) relative to that of the control group ($p < 0.05$). The content of AMPr decreases more significantly (by 1.7 times) in ME compared to that in IE.

3. Unidirectional changes in the level of AMP in the blood serum of patients with ChrE were determined – an increase in level of hBD-2 by 12.0 times in IE (2016.40 ± 109.53 pg/ml), by 5.4 times in ME (912.09 ± 30.83 pg/ml) relative to the value in the control group ($p < 0.05$). A comparison of AMP level in both clinical forms of dermatosis revealed that the value of hBD-2 in IE was 2.2 times higher than that in patients with ME.

Prospects for further research. In view of the above information, a comprehensive study of the state of innate and acquired immunity is planned, including the study of cytokine status, taking into account the clinical manifestations of dermatosis in order to justify new approaches to prognosis and increase the effectiveness of therapy for patients with IE and ME.

References

1. Reztsova PA, Vashkevich AA, Raznatovskiy KI. Lecheniye mikrobnoy ekzemy s ispolzovaniyem fototerapii: sravnitelnoye issledovaniye. *Lechebnoye delo*. 2019; 1: 82–86. [in Russian]
2. Tlish MM, Popandopulo YeK. Etiopatogeneticheskiye aspekty razvitiya mikrobnoy ekzemy (obzor). *Saratovskiy nauchno-meditsinskiy zhurnal*. 2018; 14(4): 651–656. [in Russian]
3. Udzhukhu VUy, Korotkiy NG, Davtyan YeV, Kubylinakiy AA. Optimizatsiya terapevticheskikh meropriyatiy u bolnykh nummulyarnoy ekzemy. *Rossiyskiy zhurnal kozhnykh i venericheskikh bolezney*. 2017; 20(6): 364–367. [in Russian]
4. Chalaya YeL, Sorokina YeV, Akhmatova NK. Diagnosticheskoye znacheniy narusheniy v sisteme vrozhdennogo immuniteta pri mikrobnoy ekzeme. *Rossiyskiy zhurnal kozhnykh i venericheskikh bolezney*. 2016; 19 (2): 122–123. [in Russian]
5. Yusupova LA, Yunusova YeI, Garayeva ZSh, Mavlyutova GI, Byldyuk YeV, Shakirova AN. Sovremennyye osobennosti kliniki, diagnostiki i terapii bolnykh ekzemy. *Lechashchiy vrach*. 2018: 85–87. [in Russian]
6. Hawerkamp HC, Fahy CM, Fallon PG, Schwartz C. Break on through: The role of innate immunity and barrier defence in atopic dermatitis and psoriasis. *Skin Health and Disease*. 2022; 2(2): e99. doi: 10.1002/ski2.99.
7. Huls A, Abramson MJ, Sugiri D, Fuks K, Kramer U, Krutman J, Schikowski. Nonatopic eczema in elderly women: Effect of air pollution and genes. *Journal of Allergy and Clinical Immunology*. 2019; 143: 378–385. doi: 10.1016/j.jaci.2018.09.031.
8. Kruzel ML, Zimecki M, Actor JK. Lactoferrin in a context of inflammation-induced pathology. *Frontiers Immunology*. 2017; 8: 1438. doi: 10.3389/fimmu.2017.01438.
9. Le Ngoc D, Nguyen Thi VL, ThiBich NP, Chau Van T, Ngo Minh V, Nguyen Trong H, et al. In vitro antibiotic resistance in bacterial infected eczema at Ho Chi Minh City Hospital of Dermatology. *Macedonian Journal of Medical Sciences*. 2019;7(2): 181–183. doi: 10.3889/oamjms.2019.06.
10. Leishem Y, Hajar T, Hanifin JM, Simpson EL. What the eczema area and severity index score tells us about the severity of atopic dermatitis: an interpretability study. *British Journal of Dermatology*. 2015; 172(5): 1353–1357. doi: 10.1111/bjd.13662.
11. Niyonsaba F, Kiatsurayanon C, Chieosilapatham P, Ogawa H. Friends or Foes? Host defense (antimicrobial) peptides and proteins in human skin diseases. *Experimental Dermatology*. 2017; 26: 989–998. doi: 10.1111/exd.13314
12. Prasad SV, Fiedoruk K, Daniluk T, Piktel E, Bucki R. Expression and function of host defense peptides at inflammation sites. *International Journal of Molecular Sciences*. 2020; 21: 104. doi: 10.3390/ijms21010104.
13. Presti S, Manti S, Parisi GF, Papale M, Barbagallo IA, Li Volti G, Leonardi S. Lactoferrin: cytokine modulation and application in clinical practice. *Journal of Clinical Medicine*. 2021; 10: 5482. doi: 10.3390/jcm10235482.
14. Sarmiento PM, Azanza JC. Dyshidrotic eczema: A common cause of palmar dermatitis. *Cureus*. 2020; 12(10): e10839. doi: 10.7759/cureus.10839.
15. Yemchenko YO, Shynkevych VI, Ishcheikin KY, Kaidashev IP. PPAR-gamma agonist pioglitazone reduced CD68+ but not CD163+ macrophage dermal infiltration in obese psoriatic patients. *PPAR Research*. 2020;2020:4548012. doi: 10.1155/2020/4548012

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