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https://newdaymedicine.com E:
ndmuz@mail.ru
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CLINICAL AND IMMUNOLOGICAL FEATURES OF ACNE VULGAR IN PATIENTS WITH FUNCTIONAL DYSPEPSIA *(Literature review)*

Akramova Nodira Shukhratovna https://orcid.org/0000-0002-7981-4087
Latipov Ikhtiyor Ikromovich https://orcid.org/0000-0001-5319-3828

Bukhara State Medical Institute named after Abu Ali ibn Sina, Uzbekistan, Bukhara, st. A. Navoi. 1 Tel: +998 (65) 223-00-50 e-mail: info@bsmi.uz

✓ ***Resume***

Recently, data have emerged on the role in the pathogenesis of acne development of the presence of innate immune mechanisms that contribute to the formation of skin homeostasis, the violation of which is the starting point for the appearance of acne. However, this point of view remains controversial and needs further research.

Keywords: rashes, immunity, vulgar rash, metabolism.

КЛИНИКО-ИММУНОЛОГИЧЕСКИЕ ОСОБЕННОСТИ ВУЛЬГАРНЫХ УГРЕЙ У БОЛЬНЫХ ФУНКЦИОНАЛЬНОЙ ДИСПЕПСИЕЙ *(Обзор литературы)*

Акрамова Нодира Шухратовна., Латипов Ихтиёр икромович

Бухарский государственный медицинский институт имени Абу Али ибн Сины, Узбекистан, г. Бухара, ул. А. Навои. 1 Тел: +998 (65) 223-00-50 e-mail: info@bsmi.uz

✓ ***Резюме***

В последнее время появились данные о роли в патогенезе развития угревой болезни наличию механизмов врожденного иммунитета, способствующих формированию гомеостаза кожных покровов, нарушение которых и есть отправная точка появления акне. Однако, данная точка зрения остается дискутабельной и нуждается в дальнейших исследованиях.

Ключевые слова: высыпания, иммунитет, вульгарная сыпь, обмен веществ.

FUNKSIONAL DISPEPSIYA BILAN BEMORLARDA VULGAR HUSNBUZARLARNING KLINIKO-IMMUNOLOGIK XUSUSIYATLARI

Akramova Nodira Shuxratovna., Latipov Ixtiyor Ikromovich

Abu Ali ibn Sino nomidagi Buxoro davlat tibbiyot instituti, O‘zbekiston, Buxoro, st. A. Navoiy. 1 Tel: +998 (65) 223-00-50 e-mail: info@bsmi.uz

✓ ***Rezyume***

So'nggi paytlarda harxil toshma rivojlanishining patogenezida terining gomeostazini shakllantirishga yordam beradigan tug'ma immunitet mexanizmlarining mavjudligi haqida ma'lumotlar paydo bo'ldi, ularning buzilishi vulgar toshma paydo bo'lishining boshlang'ich nuqtasidir. Biroq, bu nuqtai nazar munozarali bo'lib qolmoqda va qo'shimcha tadqiqotlarga muhtoj.

Kalit so'zlar: toshmalar, immunitet, vulgar toshma, modda almashinuvi.

Relevance

Today, the problems of treatment and prevention of inflammatory skin diseases remain the focus of modern dermatology. One of the aspects of this pathology is the so-called. skin lesions in the form of “vulgaris acne (acne vulgaris, acne).” As is known, this skin lesion is observed mainly among adolescents and young adults, affecting more than 80% of the population of this age group, then the

incidence of this skin pathology decreases markedly, only 43% of people over the age of 30 have a history of this pathology or its complications. A feature of this disease is its impact on the psychosomatic state of the patient, caused by a violation of the aesthetics of the outer integument of the face, significantly reducing the quality of life [5].

Thanks to research, this pathology, acne, is generally considered to be an inflammatory disease with a chronic course, manifested in the form of papules, pustules and inflammatory nodules on the skin [1]. And as the data of researchers show, the development of this disease is primarily based on violations of the immune defense, which explains the multifactorial nature and various symptoms of acne [3]. Pathological transformations of the immune system are also influenced by the presence of so-called on the surface of the skin. conditionally pathogenic microorganisms in the form of *Propionbacterium acne* , mites of the genus *Demodex,* various types of fungi, etc. [2]. All this together aggravates the course of the pathological process, leads to a failure in the mechanisms of formation of an adequate immune response, contributes to a change in the balance of anti-inflammatory cytokines and other inflammatory mediators, which, according to a number of researchers, leads to a chronic course of acne and the appearance of relapses that are difficult to treat [7].

The modern view of this pathology is based on the mechanism of formation of the inflammatory response due to the triggering of a cytokine reaction [7, 9]. The chain reaction of anti-inflammatory mediators and cytokines is caused by the direct influence of the cellular components of the *Propionbacterium acne wall* on specific toll-like receptors of tissue macrophage membranes. Among the inflammatory markers, IL-1, cytokines and antimicrobial peptides play an important role in the immunogenesis of acne. Other etiopathogenesis factors also play an important role, such as a pronounced imbalance of sex hormones, leading to androgen stimulation, a further increase in *Propionbacterium acne colonies, and* follicular hyperkeratosis [8]. However, some researchers refute the opinion about the central link of pathogenesis in the form of a cytokine reaction, justifying it by the presence of various clinical forms of acne [17], the development of comorbidity with background somatic pathology, primarily of the gastrointestinal tract , because it is the disturbances of the digestive processes that primarily affect condition of the skin [12].

As is known, acne (acne - acne vulgaris) is one of the main dermatological pathologies, affecting mainly adolescents and young adults, with the incidence varying from 73.4% to 96% [13]. Very often, due to its multifactorial nature, it acquires a chronic course, with varying degrees of damage to the pilosebaceous follicles, causes deep transformations of the skin, changes the psycho-emotional state of the patient, and the quality of life noticeably decreases [14]. As studies have shown, the highest incidence occurs in the age group of 15-16 years, with the onset of the first signs at 11-12 years old. Gender characteristics should also be noted - the onset of the manifestation of the main symptoms in young men occurs much later [7]. At the same time, one of the main distinguishing features of acne is its persistent recurrence of the course, the ineffectiveness of the treatment, all this is due primarily to the complexity of the pathogenesis, its multifactorial etiology. In this case, the first to emerge are violations of the immunological mechanisms of the development of the inflammatory response, caused by changes in the functioning of the central nervous system, the autonomic nervous system, damage to the gastrointestinal tract, which together lead to pathological transformations of the microbiocenosis, endocrine and other comorbid pathologies [5]. Unfortunately, despite a number of studies conducted, there is no exact picture of the stages of implementation of pathogenetic changes in acne.

As shown by the analysis of currently available scientific periodicals, many issues of socio-epidemiological and clinical changes in this pathology remain outside the field of view, while many aspects are contradictory [6]. According to the traditional hypothesis, one of the main factors in the development of inflammatory processes in pilosebaceous follicles is colonization by *Propionibacterium acnes* ***(****P. acnes*), although this strain of microorganisms itself is a resident form of the existing microflora. Based on this postulate, the dominant role in the pathogenesis of acne formation, the presence of this strain is very controversial [3]. There is another assumption that it is the subclinical inflammation of the pilosebaceous follicles that is the starting point for the formation of dermatosis [6]. In this case, there is an activation of immunocompetent cells, an increase in the number of anti-inflammatory cytokines, the expression of IL-1α, E-selectin [3], all this together changes the forms of interaction between the microorganism and the organism as a whole.

As is known, one of the factors of external protection of the body from environmental factors and the preservation of hemostasis is the skin. At the same time, changes in all homeostasis parameters,

including immunological response factors, are one of the reasons for the development of acne. A special role in this case is given to changes in TLR parameters; in particular, activation of the expression of TLR2 and TLR4 is observed [14]. As it has been determined, TLR receptors are one of the important components of the formed innate immunity, because it is thanks to them that the activity of pathogenic strains of the microorganism is suppressed. According to a number of researchers, there is a significant relationship between the degree of development of acne and the number of TLR2 secreting cells [19]. It is obvious that Toll-like receptors are activated upon direct contact with pathogen-associated molecular patterns (PAMPs) *of P. acnes.* As is known, this type of pathogen is practically invulnerable to immune cells (microphages, neutrophils), so in this case the innate immune system is triggered, which is based on Toll-like receptors of immunocompetent cells.

According to researchers, the observed mutations in the genes of immunocompetent cells of Toll-like receptors can lead to a distortion in the formation of the correct immune response to the aggression of a pathogenic strain, the entire regulation of inflammation in all its links is disrupted, leading to increased susceptibility of the body to infectious agents. In particular, with acne there is an activation of the secretion of pro-inflammatory cytokines, increased migration of lymphoid cells into the surrounding tissue, and increased permeability of microvascular walls. Further, a decrease in the functional activity of TLR-2 is observed, leading to even greater persistence of the pathogen, and the entire spectrum of the cytokine cascade is evident, leading to chronic inflammation in it, i.e. a classic picture of a vicious circle is formed [17].

A lot of research has been carried out in this direction, which has brought clarity to the understanding of the essence of the development of acne, the dominant role of *P. acnes* . Activation *of P. acnes* leads to increased secretion of cytokines such as IGF-1, IGF-1R, IL-1, IL-1β, IL-8, IL-12, which further leads to the induction of TLS, filaggrin and integrin [18]. Also, this pathogen with an activation mechanism TLR-2 (toll-like receptor 2, CD282) and TLR-4 (toll-like receptor 4, CD284) against the background of increased activity of a group of interleukins (IL-1 α, IL-1β, IL-6, IL-8, IL-12, IL-12p40, IL23p19), as well as tumor necrosis factor (TNF-α, TGF-β) 21]. And according to researchers, the increased concentration of TLR-2 and TLR-4 in the skin, as well as in the blood of patients with varying degrees of acne, leads to increased synthesis of inflammatory mediators, in particular interleukins (IL-1, IL-1β, IL-8) and tumor necrosis factor (TNF-α) through the MyD88-dependent signaling pathway [20].

Based on the above, it can be stated that with the development of acne, the expression of the entire TLS complex, in particular TLR-2 and TLR-4, increases, which leads to a pronounced innate immune response by triggering the entire pro-inflammatory cytokine cascade. In this case, a special role is assigned to TLR9; it is this representative of this family that activates the mechanisms of innate immunity by recognizing pathogenic microorganism wall pathogens [20]. And as our analysis of the literature showed, there is practically no data on studies of TLR9 in the practice of skin diseases, in particular acne. There is evidence of increased TLR9 expression during skin fibrosis in patients with scleroderma [12]. There is also data on the activation of TLR9 when inhibiting the replication processes of HPV - human papillomavirus when using a keratinocyte culture [18].

When encountering pathogenic strains of microorganisms, *P. acnes PAMP is activated,* i.e. the innate immune system is triggered, in particular Toll-like receptors. TLR receptors are one of the important components of the formed innate immunity, because it is thanks to them that the activity of pathogenic strains of microorganisms is suppressed. Mutations in the TLR genes lead to a distortion in the formation of the correct immune response to the aggression of a pathogenic strain, the entire regulation of inflammation in all its links is disrupted, leading to increased susceptibility of the body to infectious agents. In particular, with acne there is an activation of the secretion of pro-inflammatory cytokines, increased migration of lymphoid cells into the surrounding tissue, and increased permeability of microvascular walls. All this together leads to activation of the infectious agent and increased susceptibility to it [10] .

With acne, the follicles of the epithelial layer rupture and the contents of the sebaceous gland are released into the surrounding dermis, promoting the development of pustules, papules, nodules and cystic formations. Depending on the main components of the inflammatory process in the dermis, one or another type of acne develops. Thus, with neutrophil infiltration, a purulent pustule is formed; with the predominance of lymphoid cells, such as T-helper cells, papules, nodes and cystic formations appear on the dermis. The severity of scar changes depends on the strength and intensity of the immune response; the stronger the inflammatory reaction, the stronger the intensity of scar formation [19].

In the pathogenesis of acne development, 4 separate processes can be distinguished, which together determine the course and severity of this pathology: 1) expression of pro- and anti-inflammatory mediators; 2) pathological changes in keratinization processes; 3) increased production of sebaceous glands due to increased sensitivity to androgens; 4) an increase in the number of *P strains* . *Acnes* followed by colonization of skin follicles. This is confirmed by the research of V. Ryabova et al. (2017), the dominant role of activation of Toll - like receptors in keratinocytes and macrophages was shown ; we would also like to emphasize that hyperkeratinization of the follicular apparatus is caused by increased expression of cytokines C D 4+ and interleukin-1 [23] .

Another aspect of the pathogenesis of the immune response in acne is changes in the functioning of adaptive immunity mechanisms [14]. So, according to the research of A.V. Samtsova (2014) in patients with acne there is a slight increase in leukocytes, the population of T-lymphocytes (CD-3), CD-4, B-lymphocytes (CD19, CD22) against the background of a decrease in the indicators of CD-8, T-killers. In the case of chronic dermatosis, the concentration of IgE increases [17].

Microscopic examination of skin biopsies of patients with acne showed that the observed changes in the quantitative parameters of inflammatory markers, such as increased expression of E-selectin, IL-1, CD3+, CD4+, lymphoid cells (lymphocytes, macrophages) are noted not only in the skin lesion area, but also in areas without visible inflammatory processes [7].

The population of T-helper cells in the form of Th17 plays an important role in the formation of inflammatory response mechanisms in the area of acne of varying severity, up to persistent, untreatable forms of acne, this is confirmed by these studies by Sardana K. et al. (2017). At the same time, the author emphasizes that with “complex” forms of acne or so-called. Late-onset Th17 acne has an unstable form, and often undergoes a change in phenotype and transformation into other subtypes, such as IL-17-IFNγ-T cells and IL17-IL-4-T cells, i.e. factors of adaptive immunity are formed [15].

In the works of E.P. Nakhod (2009), skin biopsies from acne areas speak of the so-called. T-cell failure against the background of a significant decrease in inflammatory markers CD3+, CD4+, CD8+ lymphoid cells and serum IgA levels against the background of increased expression of activation markers of immunocompetent cells (CD25+, CD38+, HLA-DR+), as well as T-killer and B-lymphocytes [8]. In more than half of the patients, in addition to the activation of immunoglobulins of the IgA and IgG classes, disturbances in the functional activity of B-lymphocytes are detected, i.e. There is a direct correlation between the values of immunity disorders and the severity of dermatotosis.

In case of detection of inverse forms of acne, an increase in CD209+DCs, CD3+T cells, CD18+ cells and CD68+ macrophages was detected, while the number of CD56 is insignificant [19]. Also, a number of studies have shown gender differences in immune responses to acne. Thus, in males, the values of GM-CSF in comedones are significantly increased, but the indicators of a number of cytokines (IL-3, IL-10, IFN-γ) do not have such differences, the indicators of TNF-α and TGF-β are significantly increased. A correlation has also been identified between the severity of acne, the formation of scarring on the one hand, and TGF-β values on the other [16].

In males with 1st degree of severity of acne, a blood test reveals dysgammaglobulinemia, deficiency of IFN-γ, IL-3, IL-10 and IL-12p40, a decrease in CD3+ and IgA, against the background of an increase in TNF-α levels, the level of IgG class immunoglobulins, IgM, IgE, HLA-DR+ activation. When analyzing the contents of affected comedones, there was a deficiency of Th-2 type of immune response, GM-CSF, IL-10, IFN-γ.

The second degree of severity is characterized by increased synthesis of TNF-α with a decrease in the levels of IgG and IgA, CD4+, CD8+ and IL-4. The third degree of acne damage occurs against the background of increased secretion of TNF-α, pronounced IgA deficiency, activation of CD25+, locally in the comedones there is a significant lack of IL-3, GM-CSF, in the salivary fluid against the background of a decrease in interleukin IL-10, IL-13 occurs an increase in IL-3/IL-10, GM-CSF /IL-10, and, notably, hyperproduction of salivary slgA is noted [11].

Conclusions

Retrospectively, the rate of simultaneous detection of acne and pathology of the gastrointestinal tract, in particular functional dyspepsia, is 28.6% of the total number of patients with acne in a dermatological hospital. In 80.2% of cases, the development of functional dyspepsia was caused by H. Pylori infection.

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