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The role of innet immunity in the pathogenesis of psoriasis

Objective — to investigate immunohistochemical changes in the skin of patients with psoriasis.

Materials and methods. An immunohistochemical study of biopsy material taken from areas of psoriatic skin rash and intact skin in patients with psoriasis was conducted. In addition, to compare the results of the corresponding immunohistochemical researches, a study of biopsy material from the skin of the anterior abdominal wall in practically healthy individuals of the corresponding age (5 patients) was conducted, taken after surgery, in particular, hernioplasty. To determine the nature and prevalence of local cellular immune and inflammatory reactions in the skin of patients with psoriasis, immunohistochemical methods were used with determination of the expression of immune inflammation markers. The obtained immunohistochemical preparations were analyzed using an Olympus BX 51 microscope, an Olympus C 5050 Z digital camera, and Olympus DPSoft software. Immunohistochemical studies were performed at the Institute of Pathology, Carl Thiem Klinikum (Academic School of Charité, Cottbus, Germany).

Results and discussion. Analysis of the immunohistochemical study results of biopsy specimens from psoriatic skin lesions and unaffected skin areas in patients with psoriasis revealed alterations in the immunohistochemical expression of pro-inflammatory biological markers. These changes were observed both in psoriatic skin lesions and in unaffected skin regions. The findings of the study highlight the significant role of immunecompetent cell activation in the pathogenesis of the psoriatic skin process.

Conclusions. It has been demonstrated that one of the mechanisms of exacerbating inflammatory responses in patients with psoriasis is the activation of immunecompetent cells, particularly through TL receptors. Further indepth studies of immunohistochemical changes in proinflammatory biological markers in the skin of psoriasis patients will contribute to a deeper understanding of the pathogenesis of the psoriatic process.

Keywords

Psoriasis, immunohistochemical changes in the skin, toll-like receptors, immunological changes.

Currently, psoriasis is considered a systemic disease of the body in which functional and organic changes occur in a number of organs and systems, including the gastrointestinal tract, hepatobiliary system, cardiovascular system and a number of others. Despite numerous studies, the etiology of psoriasis remains unclear, and a number of questions regarding the pathogenesis of this dermatosis are also unresolved. At present, it is possible to identify certain leading factors and mechanisms of psoriasis development, in particular immunological and genetic [15].

It is generally accepted that the occurrence of inflammation in the skin in patients with psoriasis begins with the activation of skin cells. The role of activated skin cells is not only in the initiation of a «pre-immune» inflammatory process in response to the penetration of an unknown antigen, but also in the involvement of immune system cells. The immune system is involved in the development of the inflammatory process much later, after the penetration of an unknown pathogen through the skin. During this time, pathogens do not «travel» freely

throughout the body, as they are recognized as «foreign» by keratinocyte structures. In the mid-1990s, a number of authors defined this «foreign» as pathogen-associated molecular patterns (PAMPs) that are absent in multicellular organisms [10, 13].

PAMPs are recognized by so-called toll-like receptors (TLRs) [14]. TLRs are transmembrane protein structures that consist of membrane and cytoplasmic regions. Currently, 13 types of toll-like receptors are known, of which 11 are the most studied [9, 11, 12].

The first toll receptor family was discovered in the fruit fly Drosophila melanogaster in 1992 [1] as a component involved in embryonic development of Drosophila. Later, the toll receptor was found to be involved in the immune response in adult flies [2]. Drosophila mutants in the Toll gene were susceptible to fungal infections. Further studies have shown the presence of homologues of the Drosophila toll receptor in mammals, which are called toll-like receptors [3—5]. In humans, most TLRs are expressed by macrophages, monocytes, neutrophils, and there is also evidence of their presence on intestinal epithelial cells, vascular endothelium, and skin keratinocytes [6]. Stimulation of TLRs contributes to the formation of a temporary signaling multicomponent structure that induces the cell genome to produce cytokines, adhesion molecules, and costimulatory molecules that regulate the activation of adaptive immunity.

In the case when activated skin cells cannot independently destroy the pathogen and ensure the interruption of «pre-immune» inflammation, cells of the immune system are included in the process.

The study of the role and function of TLRs in human skin has been carried out relatively recently. A number of authors believe that TLRs of activated keratinocytes are able to model the adaptive immune response [7]. Some studies have shown that TLR-stimulated keratinocytes of the supernatant are able to induce dendritic cell maturation [8]. Activation of TLRs has been found in some skin diseases of infectious etiology.

Thus, the study of TLRs expression by skin cells is important for a deeper understanding of the mechanism of immune inflammation in the skin of patients with psoriasis.

Objective — to investigate immunohistochemical changes in the skin of patients with psoriasis.

Materials and methods

In patients with psoriasis, a double biopsy study was performed, in particular from areas of skin affected by psoriatic rash and from areas of intact skin. In addition, to compare the results of the immunohistochemical study, a study of biopsy material of the skin of the anterior abdominal wall in practically healthy individuals of the corresponding age (5 patients), taken after surgery, in particular hernioplasty. Fragments of the skin biopsy material were fixed in 10 % neutral formalin. Subsequently, the biopsy material was processed in alcohols and embedded in paraffin blocks, from which histological sections 4—6 μm thick were prepared. When setting up immunohistochemical reactions in order to unmask antigens, heat treatment of sections was performed and blocking of nonspecific protein binding with the DAKO protein block and endogenous peroxidase activity with the DAKO peroxidase block, after which primary antibodies were applied. Using the DAKO EnVizion + detection, visualization of primary antibodies was performed. Histological structures for visualization of immunohistochemical preparations were stained with Mayer's hematoxylin, covered with Canada balsam and covered with coverslips. After that, positive reactions were recorded based on the number of cells that had a clear positive reaction, taking into account the intensity of the staining. Cells with positive expression were studied in 4—6 random fields of view of the microscope. The results of immunohistochemical reactions were evaluated by counting cells with positive staining in 10 randomly selected fields of view of the microscope at a magnification of 400. The degree of staining intensity was assessed: 0 — absence of staining, 1 (+) — weak staining of light brown color, 2 (++) — moderate staining of brown color, 3 (+++) — pronounced staining of dark brown color. The results of the immunohistochemical reaction were evaluated by a semi-quantitative method in scores from 0 to 6 according to the generally accepted method, taking into account the stained cells. 0 points were determined in the absence of staining, 1 point — up to 10 %, 2 points — up to 20 %, 3 points — up to 30 %, 4 points — up to 40 %, 5 points — up to 50 %, 6 points — more than 50 % of stained cells.

To determine the nature and prevalence of local cellular immune and inflammatory reactions in the skin, immunohistochemical techniques were used to determine pro-inflammatory markers of immune inflammation.

The obtained immunohistochemical preparations were studied using an Olympus BX 51 microscope, an Olympus C 5050 Z digital camera, and Olympus DP-Soft software. Immunohistochemical studies were performed at the Karl-Thiem-Klinikum Institute of Pathology (Charité Academic School, Cottbus, Germany).

Results and discussion

In the examined patients with psoriasis vulgaris, a double study of biopsy material taken from areas of

skin affected by psoriatic rash and areas of intact skin was conducted. In biopsies from areas of intact skin of patients with psoriasis, the phenomena of hyperkeratosis, focal dyskeratosis and edema of the epidermis were observed. In the basal parts of the epidermis, increased proliferative activity was noted, the formation of microplaques was observed, and in the underlying dermis — mild inflammatory infiltration. Ingrowth of vessels into the papilla of the dermis with detachment of the epidermis and the formation of microerosions was also observed. Immunohistochemical study of biopsies from areas of intact skin of patients with psoriasis revealed structural changes that indicated the presence of immunocompetent cells in the papillary layer of the dermis. At the base of the papillae, mild inflammatory infiltrates were observed, consisting mainly of CD4-positive lymphocytes. The greatest activity of these lymphocytes was recorded in inflammatory perivascular infiltrates of the dermis. A similar localization of CD8-positive cells was also determined. In areas of intact skin, single CD20 and CD56-positive cells were detected. Perivascularly, at the base of the papillae and in the papillae themselves, a significant number of CD68-positive cells were determined.

In immunohistochemical reaction to TLR2 in patients with psoriasis, in areas of intact skin, a positive reaction with nuclear expression patterns in macrophages, epidermal dendritic cells and in the endothelium of blood vessels of the dermis was determined. When setting up a reaction to detect TLR4 expression, intense and widespread nuclear and cytoplasmic staining of cells of all layers of the epidermis, including in the stratum corneum, was determined.

When studying the expression of TLR9 in areas of intact skin of patients with psoriasis, a significant number of TLR9-positive epithelial cells were found in all layers of the epidermis, including the superficial ones, a diffuse reaction in the cells was observed, which was characterized by both nuclear and cytoplasmic staining. TLR9 expression was also detected in single inflammatory cells and their small clusters in the papillary layer of the dermis. The results of the immunohistochemical reaction indicate that in areas of intact skin of patients with psoriasis with a progressive stage of the course there is hyperproduction of toll-like receptors, which is the basis for the development of the reaction of immunocompetent cells and the formation of new morphological elements of the psoriatic rash. Morphological studies of skin biopsies taken from patients with psoriasis with a progressive stage of dermatosis from areas affected by psoriatic rash indicated the presence of a complex of inflammatory, hyperplastic and dysregenerative reactions. In particular, in these areas of the skin, thickening of the epidermis, excessive formation of keratin, an increase in the number of papillae that penetrated deeply into the epithelial layer were observed. Papillomatous hyperplasia was observed in the epidermis. Epithelial cell proliferation occurred directly around the papillae. A «cap» of a strip of swollen epithelial cells and a zone of intercellular edema was formed around the apex of the papillae in the epidermis. Tangential small hemorrhages were observed in the lower layers of the stratum corneum, which was caused by damage to the apex of the papillae. The presence of blood in the stratum corneum of the epidermis has been established and can serve as a nutrient medium for microorganisms and is likely to play a role in the formation of Munro microabscesses. Perifocally in areas of skin affected by psoriatic rash, intercellular edema with acanthosis was observed. Destructive-dystrophic changes were recorded in epithelial cells, as well as the presence of lymphoid cell destruction in areas.

A characteristic morphological sign of the activity of the psoriatic process is the presence of inflammatory infiltrates in the papillary layer of the dermis and directly in the papillae. It should be noted that these perivascular infiltrates at the base of the papillae consisted mainly of lymphoid cells and macrophages. In the lumen of the lymphatic vessels, through which lymph flows from the papillae, a significant number of large macrophages with granular cytoplasm are found. At the base of the papillae and directly in the papillae, proliferation of epithelial cells and fibroblasts was observed, in the presence of chronic inflammatory cells, with the formation of a vascular cord. In the papillary layer of skin areas affected by psoriatic rash, the formation of «muffs» around the vessels was observed. Newly formed blood vessels were also detected in these areas. A capsule of collagen fibers was detected around the «muffs». Morphologically, the papilla consisted of a sheath of collagen fibers and several blood vessels located in the center of the papilla. Several lymphatic vessels were detected perivascularly, through which intercellular fluid and lymph flowed from the apex of the papilla and the swollen epithelial layer. A significant number of large macrophages with granular cytoplasm were detected in the lumen of these lymphatic vessels. The walls of blood vessels in the areas of skin affected by psoriatic rash looked intact, with the exception of signs of slight edema, which indicates the absence of immune reactions in them, and also, accordingly, indicates the absence of components of immune reactions in the blood plasma. It should be noted that the components of the vascular bundle, which extends from the vascular plexus at the base of the papilla to the papilla itself, are arterial, venous and

lymphatic vessels. It is through the lymphatic vessels that potential antigens and mediators flow from the epithelial layer, to which lymphoid cells and macrophages can react. The corresponding reaction in the form of infiltrates was observed in areas immediately adjacent to the lumens of the lymphatic vessels at the base of the papillae. The presence of inflammatory cells (lymphoid elements, macrophages) in the lumens of the lymphatic vessels and in the interstitium nearby was also established. In the lymphatic system, lymphostasis and expansion of the lymphatic vessel network were observed both in the papillae and in the collector vessels in the papillary layer of the dermis.

Our studies allow us to assume that significant thinning, swelling and loosening of the epithelial layer contribute to its easy damage and penetration of external, pathogenic infectious factors into the papillary tissue. As a result, Munro microabscesses occur. In the reticular layer of the dermis of areas affected by psoriatic rash, inflammatory infiltration was focal, in particular only in the upper parts of the dermis, which border the papillary layer. The results of our relevant studies indicate that in the progression of the skin psoriatic process, antigens penetrate the dermis from the epithelial layer. This is confirmed by the fact that the most pronounced chronic inflammatory infiltrates are found at the base of the papillae, where lymph flows from the epithelial layer and where the collecting lymphatic vessels are located. The data obtained indicate that immunopathological processes occur not in the walls of blood vessels, but in the interstitium, in particular, in and around the lymphatic vessels. This indicates that in the morphogenesis of the skin psoriatic rash, the processes of proliferation of connective tissue elements, primarily vascular, as well as the epidermis itself, play a significant role.

Immunohistochemical studies of skin areas affected by psoriatic rash in patients with psoriasis with a progressive stage of the course allowed us to identify a complex of structural changes that indicate the significant importance of immunopathological reactions in the pathogenesis of this dermatosis. In particular, inflammatory infiltrates were detected in the areas of psoriatic skin rash, which were localized in the papillary layer of the dermis and on the border of the papillary and reticular layers of the dermis. A significant number (up to 50 %) of CD4-positive cells were determined in them, which indicates the presence of induced T-helpers. CD4-positive cells were also detected in the papillae of the dermis. The bulk of CD4-positive cells was detected in perivascular infiltrates at the base of the papillae, where their number was up to 40 % of the entire pool of inflammatory cells. The proportion of

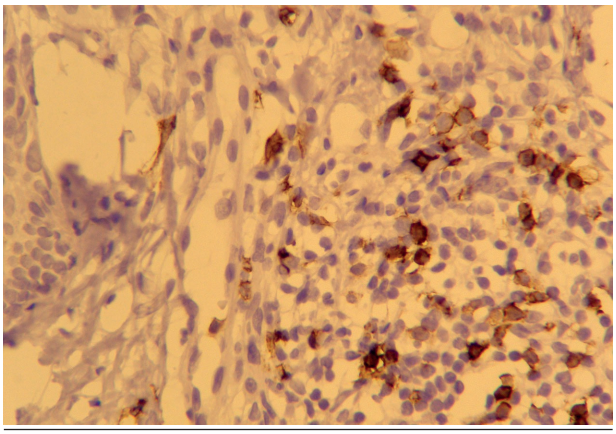

Fig. 1. **Psoriatic plaque. A significant number of CD8-positive cells in the inflammatory infiltrate in the papillary layer of the dermis.** × 400

CD8-positive cells in the inflammatory infiltrates of the dermis was up to 30 %, most of these cells were found at the base of the dermal papillae. Active migration of CD8-positive cells from the papillae into the epithelial layer was also established. An increase in the number of CD8-positive cells was observed in areas of epidermal destruction, which was accompanied by leukocyte infiltration (Fig. 1).

This indicates the cytotoxic effect of CD8-positive cells in relation to epithelial cells. Close contacts of CD8-positive cells and epithelial cells were observed mainly in the germinal zone in the areas of the tips of the papillae. At the same time, epithelial cells with which CD8 cells contacted contained enlarged nuclei, where one or more nucleoli were detected. These changes in the nuclei of epithelial cells indicate the presence of antigenic components in them.

In areas of the skin affected by psoriatic rash, in particular, in the inflammatory infiltrates at the base of the papillae and their tips, a small number of CD20-positive cells were detected. Migration of these cells into the epithelial layer was not detected. CD56-positive cells were also detected in the inflammatory infiltrates of the dermis (Fig. 2).

Their number was insignificant and amounted to 1—2 % of the total number of inflammatory cells in these areas. In inflammatory infiltrates in the dermis, in particular, at the border of the papillary layer and in the papillae, especially their tips, CD68-positive cells were detected. Their number was up to 10 % of the total number of cells in the inflammatory infiltrate. The perivascular location of CD68-positive cells and signs of their migration from the papillae to the dermis and in the opposite direction along the lymphatic and blood capillaries were also observed. In inflammatory infiltrates in the dermis, contacts of CD68-positive cells with lymphoid elements were observed. Migration of CD68-positive cells into the epithelial layer to the surface areas of the epidermis was also detected (Fig. 3).

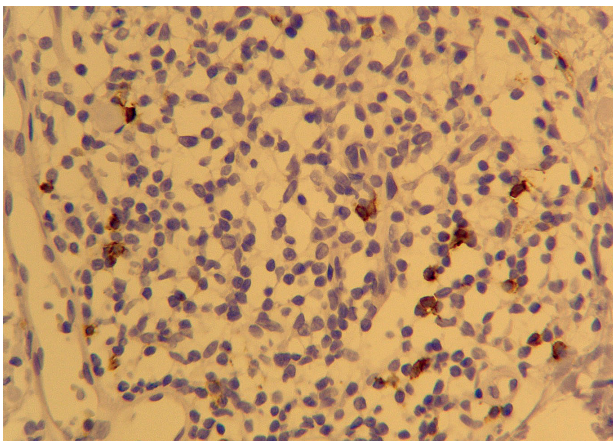

Fig. 2. **Psoriatic plaque. CD56-positive cells in infiltrates of the papillary layer of the dermis.** × 400

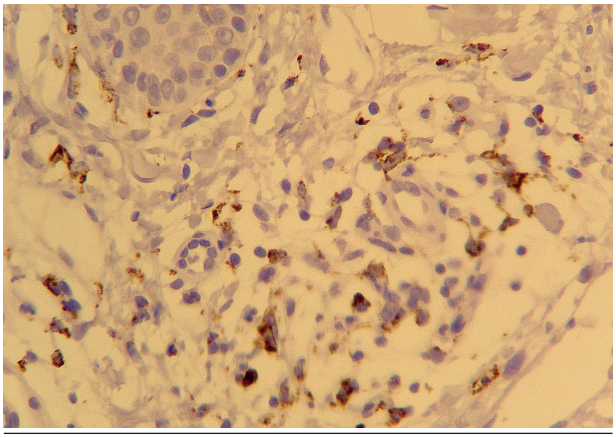

Fig. 3. **Psoriatic plaque. CD68-positive cells in perivascular infiltrates of the papillary dermis.** × 400

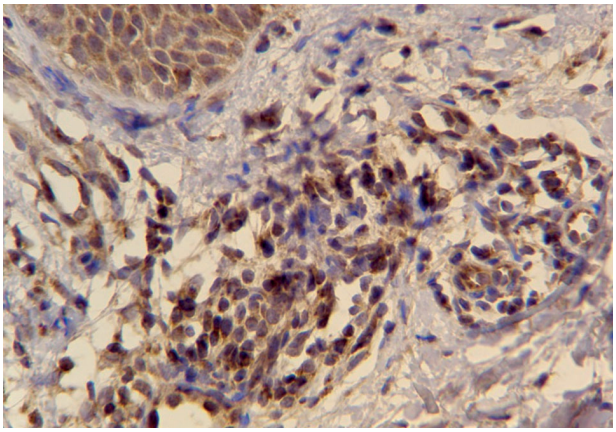

Fig. 4. **Area of psoriatic skin rash of a patient with psoriasis. Membrane expression in macrophages of dermal papillae and macrophages migrating into the epithelial layer. Reaction to detection of TLR4 expression.** × 400

We also performed immunohistochemical reaction to detect the expression of TLR2, TLR4 and TLR9 receptors in areas of psoriatic skin rash before treatment. When studying the expression of TLR4, a background diffuse cytoplasmic and nuclear staining of epidermal cells, vascular endothelium and single macrophage cells was detected. The number of positively stained epidermal cells was up to 80% (Fig. 4).

The most intense staining was observed in macrophages located in the papillae and perivascularly in the dermis. Immunohistochemical reaction with TLR2 revealed a less intense diffuse background staining of the epidermis, vascular endothelium and part of the cells in inflammatory infiltrates of the dermis. In areas of psoriatic rash, distinct membrane expression of TLR4 was established by numerous macrophages of the dermal papillae. The phenomenon of positive nuclear membrane staining of epithelial cells bordering the keratinized masses on the skin surface was detected. In the papillary layer of the dermis, a characteristic membrane expression of TLR4 was detected, both in individual macrophages located perivascularly and as part of perivascular inflammatory infiltrates. The localization of macrophages in lymphatic vessels flowing from the tip of the papillae to their base, where there is a cluster of vessels, was topographically traced. A situation is created when the ligands of microorganisms can freely penetrate the papillary layer and react with macrophages. The latter actively migrate to the tip of the papillae and even penetrate the epithelial layer. At the same time, macrophages are activated, increase in size, and actively express TLR2 and TLR4 receptors. It is obvious that macrophages, after activation, migrate to the base of the papillae, where they are included in the inflammatory infiltrates located perivascularly. In these areas, the main interactions of macrophages and lymphoid cells occur.

Immunohistochemical studies of TLR9 expression in skin areas affected by psoriatic rash revealed significant expression of TLR9 in inflammatory infiltrate cells in the papillary dermis and epidermis. It was found that macrophages migrating in the vessels of the papillae of the dermis had a distinct positive expression of the marker. TLR9-positive macrophages and monocytes were found in the vessels and perivascular space of the papillary dermis. TLR9-positive cells were also found in the epidermis in areas of edema. Epitheliocytes showed weak and moderate nuclear and cytoplasmic reactions. It was established that some of the TLR9-positive cells in the epidermis are migrants from the papillary layer of the dermis. Such cells include macrophages and activated lymphoid elements, as well as neutrophilic granulocytes. The latter show positive staining, especially in areas of formation of Munro microabscesses under the stratum corneum. Considering that at the stage of progression in areas of psoriatic skin lesions edema, acanthosis and desquamation of epithelial cells occur, a passage is formed

through which bacterial microflora penetrates. When conducting immunohistochemical studies, positive expression of TLR9 was established in colonies of microorganisms, intracellularly in granulocytes and in macrophages under the condition of their phagocytosis. At the same time, in the areas of Munro microabscesses in the adjacent papillae of the dermis, the largest number of sharply TLR9-positive granulocytes and macrophages was detected.

Analysis of the results of the relevant studies allows us to assume that part of the TLR9-positive material moves from the epithelial layer into the lymphatic drainage, the cytoplasm of phagocytic cells, which migrate back into the dermis and activate inflammatory reactions. With the progression of the psoriatic process, there is a significant migration of macrophages into the basal parts of the epidermis and contacts of these cells with TLR9-positive epithelial cells. In addition, a certain amount of TLR9-positive granular material was detected in the perivascular spaces of the papillary layer of the dermis, which was located extracellularly, in particular in the areas of the tips of the papillae. Thus, the hyperproduction of this biological marker in the epidermis is accompanied by its entry into the dermis through lymphatic collectors or as part of phagocytes.

Conclusions

The inflammatory process in the skin in psoriasis develops as a result of immunopathological reactions, as evidenced by the predominance of immunocompetent cells in inflammatory infiltrates. The most represented in the corresponding psoriatic inflammatory infiltrates is the cellular link — CD4, CD8, CD68.

In the elements of the skin psoriatic rash, two poles of concentration of immunocompetent cells are noted, in particular — in the papillae of the dermis on the border with the epidermis and in the epidermis itself, as well as in the dermis — in the perivascular spaces at the base of the papillae. Obviously, the corresponding features are associated with the places of concentration of antigens.

Migration of immunocompetent cells, primarily — CD4, CD8, CD68, into the epithelial layer up to the superficial horny masses, was detected. Also, a significant number of CD68+ cells migrate along the papillae in the opposite direction — from the epidermis to the dermis (along the lymphatic capillaries).

In patients with psoriasis, hyperproduction of pro-inflammatory biological markers by skin epithelial cells, in particular TLR2, 4, 9-positive cells, has been established. In this case, the corresponding TLR-positive cells are detected both in areas of skin affected by psoriatic rash and in areas of intact skin. At the same time, the number of corresponding cells in areas of skin with psoriatic plaques was higher compared to their number in areas of intact skin.

In patients with psoriasis, hyperproduction and hypersecretion of pro-inflammatory biological markers by skin epithelial cells, in particular TLR2, 4, 9-positive cells, has been established. At the same time, the corresponding TLR-positive cells are found both in areas of skin affected by psoriatic rash and in areas of intact skin. However, the number of corresponding cells in areas of skin with psoriatic plaques was higher compared to their number in areas of intact skin.

TLR2-, TLR4- TLR9-positive macrophages after their activation in the dermal papillae migrate to the base of the papillae, where they are included in the inflammatory infiltrates located perivascularly. In these areas, the main interactions of macrophages and lymphoid cells occur.

There is no conflict of interest.

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Роль вродженого імунітету в патогенезі псоріазу

Мета роботи — дослідити імуногістохімічні зміни в шкірі хворих на псоріаз.

Матеріали та методи. Проведено імуногістохімічні дослідження біопсійного матеріалу, взятого з ділянок шкірної псоріатичної висипки та інтактної шкіри у хворих на псоріаз. Крім того, для порівняння результатів відповідних імуногістохімічних досліджень проведено вивчення біопсійного матеріалу зі шкіри передньої черевної стінки у практично здорових осіб відповідного віку (5 пацієнтів), взятого після оперативного втручання, зокрема герніопластики. Для визначення характеру і розповсюдженості місцевих клітинних імунних і запальних реакцій у шкірі хворих на псоріаз застосовували імуногістохімічні методики з визначенням експресії маркерів імунного запалення. Отримані імуногістохімічні препарати досліджували на мікроскопі Olympus BX 51, цифровому фотоапараті Olympus C 5050 Z та програмному забезпеченні Olympus DP-Soft. Імуногістохімічні дослідження проводили в Інституті патології Карла-Тіема-Клінікум (Академічна школа Шаріте, Котбус, Німеччина).

Результати та обговорення. З урахуванням аналізу результатів імуногістохімічних досліджень біопсійного матеріалу з ділянок шкіри псоріатичної висипки та інтактної шкіри у хворих на псоріаз встановлено зміни імуногістохімічної експресії прозапальних біологічних маркерів як у вогнищах шкірного псоріатичного ураження, так і в ділянках інтактної шкіри. Результати проведених досліджень вказують на вагоме значення активації імунокомпетентних клітин у патогенезі шкірного псоріатичного процесу.

Висновки. Доведено, що одним із механізмів загострення запальних реакцій у хворих на псоріаз є активація імунокомпетентних клітин, зокрема через TL-рецептори. Подальші поглиблені дослідження імуногістохімічних змін прозапальних біологічних маркерів у шкірі хворих на псоріаз буде сприяти отриманню нових даних щодо патогенезу псоріатичного процесу.

Ключові слова: псоріаз, імуногістохімічні зміни у шкірі, толл-подібні рецептори, імуногістохімічні зміни.

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