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Research Article

MORPHOGENETIC CHARACTERISTICS OF KERATODERMA IN METABOLIC DISORDERS

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ABSTRACT

Studying the morphological and genetic different types of keratoses is key for correct diagnosis and choice of treatment. The association between metabolic disorders and skin diseases highlights the need for an integrated approach to the management of patients with chronic diseases, including diabetes mellitus. Further research is needed to better understand the pathogenesis and develop effective treatments.

KEYWORDS

Morphology, skin, keratoderma, diabetes mellitus.

INTRODUCTION

In our country, data on the epidemiology of keratoderma is extremely scarce, which is due to a number of reasons. Firstly, the analysis of statistical data and publications in the scientific literature is complicated by the presence of many synonyms for the disease: seborrheic wart, seborrheic keratoma, senile wart, basal cell papilloma, pigmented epithelioma, pigmented papilloma, seborrheic acanthoma, pigmented basal cell epithelioma, senile papilloma, etc. Secondly, despite the fact that this benign tumor was first mentioned by S. Pollitzer at the end of the 19th century (1890) (1,4,7), its detailed description by D.I. Golovin did it relatively recently - in 1958 (2,3). And thirdly, to date the etiology of this proliferative process

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on the skin is not clear. According to the international histological classification of skin tumors "Pathology and Genetics of Skin Tumors", published under the auspices of the International Agency for Research on Cancer (5,6,7), seborrheic keratosis is a benign epithelial tumor and is a type of acanthoma. The disease affects men and women almost equally, predominantly over 40 years of age (17). A clear correlation of its debut with age has been established. Thus, in the cohort of 24–49 year olds, the prevalence of seborrheic keratosis was 38%, in 50–59 year olds – 69%, in 60–69 year olds – 86%, and among 70–79 year olds – more than 90% (34). The disease is extremely common in countries with high levels of insolation, for example, in Australia, where it occurs in 100% of cases in the population over 50 years of age. (35).

European studies indicate a slightly lower incidence of this epithelial tumor: 82% among men and 62% among women aged over 70 years (8,9,10,37,39). Russian researchers point out that closed areas of the skin exposed to mechanical stress (friction, pressure) are most affected. In patients with numerous elements of seborrheic keratosis, a positive family history is often recorded (11,12,13,42,49). Seborrheic keratosis is represented by multiple foci of proliferative growth (14,16,21,45). Dermatoscopic and histological examination is mandatory to verify the diagnosis (15,16,23,28,29).

Seborrheic keratosis (SK) is a common benign tumor of the epidermis in men and women, occurring more often after 45-50 years. KS elements appear as distinct brown spots and/or plaques widely distributed along the edges of the skin (17,18,19,25,26). There is no unified morphological classification of this disease, since the histological manifestations of KS are varied - symptoms of several histological types may be present in the same lesion (20,25,28,29).

In foreign literature they are divided into acanthous, hyperkeratotic, adenoid, irritated, clonal type and melanoacanthomas. The diagnosis of KS in most cases is not in doubt, but the tumor can mimic other skin neoplasms: common warts, lentigines, melanocytic nevi, actinic keratosis, Bowen's disease, squamous cell carcinoma both clinically and during pathological examination (21,22,32,38). The etiology of KS is unknown, although genetics, increased sun exposure, somatic mutations in fibroblast growth factor receptor 3 (FGFR3), and human papillomavirus have been identified as risk factors (23,24,31,35). Currently, the theory of keratinocyte aging and impaired apoptosis in KS is widely accepted. Studies are rare, and the reasons for changes in the proliferative properties of cells in KS are unclear (25,26,27). In addition, MK is of interest for studying cell cycle disorders, since according to modern histological criteria it is classified as a benign tumor (28,29,30). However, many immunohistochemical features of malignant neoplasms and clinical cases of malignant transformation within MC foci make it necessary to continue the targeted study of the pathogenesis of the

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neoplasm. The main mechanism of proliferation impairment is a defect in the function of suppressor genes. In addition to high proliferation, tumor growth is associated with impaired cell ability to regulate apoptosis.

The most studied cell cycle markers that are involved in the control of the proliferative potential of any cell are p53, p21, p27 and p16. Determination of their expression level using immunohistochemical methods allows us to identify the degree of proliferation disorder, which is invariably accompanied by tumor growth, the ability of the tumor to invade and metastasize (10,12,13,14). p27 (Kip1) is an inhibitor of cyclin-dependent kinase 1B, a product of the human CDKN1B suppressor gene, a member of the Cip/Kip protein family. This protein regulates the course of the cell cycle, is responsible for its arrest in the G1 phase by suppressing the activity of the cyclin A/cyclin-dependent kinase 2 and cyclin E/cyclin-dependent kinase 2 complexes. p27 is a nuclear-cytoplasmic protein, its intracellular localization is regulated post-translational modifications. It performs its inhibitory functions in the nucleus; after its movement into the cytoplasm, further advancement of the cell through the cycle becomes possible (10,11,15). Overexpression of p27 has been studied in malignant neoplasms of internal organs and is an unfavorable prognostic factor for tumor progression (24,27,28). There are few studies on benign neoplasms, and they contain conflicting data. Thus, in a study of 10 irritated and acanthotic SCs, A. Brueks et al. (8) overexpression of only p27 was detected along with the absence of expression of p53, p16 and a low proliferative index, which allowed the authors to talk about the leading role of p27 in the control of cell proliferation. However, it seems to us appropriate to study p27 in all types of KS, taking into account their morphological diversity. As a result of the study, a violation of p27 protein expression was revealed in all histological types of KS, which indicates its significant role in the pathogenesis of the disease. Increased expression of p27, normally found in the greatest quantity in cells in the G1 phase (19,20), was found in the authors' studies in irritable, adenoid and some cases of clonal types. Considering that p27 is a "reserve brake" of cell division (12,13), its significant increase in KS may indicate the absence or insufficient response of the first link of cell cycle regulators - p53 and p16 to an increase in the proliferative activity of cells. The staining of nuclear membranes and adjacent areas of the cytoplasm was considered as a decrease in the nuclear content of p27 and its release into the cytoplasm. An imbalance between the amounts of nuclear and cytoplasmic p27 is a poor prognostic sign and is found mainly in malignant skin tumors. According to the literature (12,13,40,41,46), more than 70% of metastatic melanomas contain p27 in the cytoplasm, while melanomas without metastases contain p27 in the nucleus. The appearance of a significant number of cells with nuclear membrane staining, predominantly in the irritated and adenoid

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type of KS, indicates a greater risk of malignancy than in other histological types of tumors, where there is no membrane staining. A negative reaction during an IHC study or the detection of single positive nuclei of tumor cells in hyperkeratotic, acanthotic and clonal (in some cases) MC can be regarded, on the one hand, as the absence of significant proliferative activity of cells and the lack of inclusion of a "reserve" mechanism" in the form of p27, on the other hand, indicate a defect in apoptosis, given the slow, steady growth of elements. In none of these cases, specific staining of nuclear membranes was detected, which indicates different mechanisms of cell cycle disorders in different histological types of keratomas. Thus, morphological variants of MC have different prognosis for development, growth and risk of malignant transformation. The identified features of p27 protein expression indicate the presence of disturbances in the regulation of the cell cycle and proliferative activity of tumor cells, characteristic of each histological type of KS, which must be taken into account in a comprehensive assessment of the expression of other cell cycle markers in KS (13,45).

The role of insulin resistance in the pathogenesis of KS brings us closer to the theory of keratinocyte aging. In a study by A. Saraiya et al. in 2013, a case was described in which the appearance of multiple MCs in the absence of a genetic predisposition was associated in patients with insulin resistance and type 2 diabetes mellitus (type 2 diabetes). Thus, a major role for high insulin concentrations was suggested in stimulating DNA synthesis and cell proliferation. Also, M. Blomberg et al., based on their observations, recommended that when FGFR mutations are found and concomitant skin pathology in the form of papillary pigmentary dystrophy of the skin or multiple MCs, insulin studies are carried out in order to detect hyperinsulinemia 2. It should be taken into account that type 2 diabetes is one of the most common diseases; every 20 inhabitants of the planet suffer from it after 35–40 years. In addition, it is included in the so-called group of "old age" diseases along with ischemic heart disease, stroke, and atherosclerosis. In a study by a number of authors of 150 patients with multiple KS, type 2 diabetes occurred in 65.3% of cases (98 patients), and impaired glucose tolerance – in 24% of cases (36 patients). Such a high percentage of a combination of carbohydrate metabolism disorders and multiple KS can hardly be considered a mere coincidence, given that both diseases are genetically determined and develop in middle and old age. Interestingly, one of the possible factors in the development of type 2 diabetes is considered to be an increase in the level of p16 in the pancreas during aging, leading to inhibition of beta cell proliferation and a decrease in their ability to respond to damage, which subsequently leads to insulin resistance (50). Morphologically, 6 histological types are distinguished: acanthotic, adenoid (reticular), hyperkeratotic (papillomatous), clonal, melanoacanthoma and

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irritated. In all histological types, hyperkeratosis, acanthosis, papillomatosis, horny and pseudohorny cysts are present to varying degrees of severity. The intensity of melanin pigment varies from almost completely absent to strong. In addition, 2 rare histological types of seborrheic keratosis have recently been described - with a large amount of mucin in the cells - adamantinoid and when basaloid keratinocytes are arranged like "pseudorosettes". Currently, there is no consensus on the etiology and pathogenesis of KS. Most theories are contradictory and do not explain the essence of the pathological process and the variety of forms.

Follicular keratoses represent a disorder of keratinization and differentiation of keratinocytes, leading to the formation of keratotic plugs and parakeratotic cones that penetrate the dermis, causing perforation of the epidermis. There is no uniform classification of keratoses pilaris. There are papular, atrophying and vegetative forms (4,29,30). The etiology and pathogenesis have not been fully studied. The previously assumed role of a viral or bacterial infection, a violation of vitamin A metabolism in the development of this dermatosis is only of historical interest. A certain significance in the development of the disease, in addition to impaired carbohydrate metabolism, is attributed to liver damage (chronic hepatitis) with the development of secondary vitamin A deficiency (4.14). A genetic predisposition to the development of Kirle disease (KD) has not been conclusively proven, although cases of the disease among relatives in the same family with consanguinity (first-degree relatives) have been described. As originally defined by J. Kirle (30), it is a disease in which an atypical clone of keratinocytes penetrates through the epidermis into the dermis. It is believed that the basis of the pathological process is a violation of keratinization, differentiation and keratinization of keratinocytes (formation of dyskeratotic foci and acceleration of the keratinization process). This leads to the formation of keratotic plugs with areas of parakeratosis. Keratification begins already at the border of the epidermis and dermis. The rate of differentiation and keratinization exceeds the rate of cell proliferation, therefore the parakeratotic cone partially penetrates deeper into the damaged epidermis and causes its perforation into the dermis (4,5,43,49).

There is no uniform classification of keratoses pilaris. Among the independent nosological forms, papular, atrophying and vegetative follicular keratoses are distinguished. Some authors note the similarity of Kirle disease (KD) with lenticular persistent hyperkeratosis of Flegel, considering the latter as a variant of KD, although the clinical manifestations differ. Other authors (5,7,18) classify CD as vegetative follicular keratoses, and Flegel's disease as papular.

There is a concept of reactive perforating keratinization disorder in kidney disease, liver disease and diabetes mellitus. The concept of perforating skin

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diseases has emerged, in which the elimination of altered skin components occurs through the epidermis (transepidermal elimination). Some authors dispute the independence of CD as a nosological entity (45,47). In ICD-10, in class XII (diseases of the skin and subcutaneous tissue), CD has a subcategory L87.0 - transepidermal perforated changes.

Pathomorphologically, there are depressions in the epidermis and dilated orifices of hair follicles filled with hyperkeratotic plugs. Under the plugs, the growth of the granular layer is pronounced, and in places without hypergranulosis there is parakeratosis, penetrating to the dermis. Next, the epidermis becomes thinner and horny masses penetrate into the dermis, and inflammatory infiltrates such as granulomas are formed from lymphocytes, leukocytes, histiocytes and giant cells. Death of the sebaceous glands, degeneration of collagen fibers, and hyperelastosis are observed (49). Clinically, the onset is gradual, new rashes appear as old ones disappear. Characteristic are follicular or parafollicular papules, first the color of healthy skin, then a grayish or brownish-red hue, up to 1 cm in diameter. In the center of the elements there is a horny plug, when removed, a crater-shaped depression is formed. Papules tend to grow peripherally and coalesce, forming dry polycyclic plaques covered with scales and crusts. The consistency is dense, the surface is uneven, warty. Fresh rashes are accompanied by mild itching (more often in patients with diabetes) or do not bother. Old lesions are painful when pressed. Localization of rashes - extensor surfaces of the limbs, torso, buttocks. Koebner phenomenon and secondary infection are possible (30). The mucous membranes are not affected, and rashes on the palms, soles, genitals and mouth are rare. The course of Kirle disease (KD) is chronic and relapsing, treatment is difficult, and the prognosis depends on the underlying disease. Diagnosis is based on history, clinical and histological picture. Differential diagnosis includes Devergy's lichen pilaris, Darier's follicular dyskeratosis, Mibelli's porokeratosis, elastosis perforating creeping, reactive perforating collagenosis and Flegel's disease (31,32).

Flegel's disease, like CD, a rare form of keratosis pilaris, is associated with impaired synthesis of keratin 55K. Histologically, thinning of the epidermis, follicular orthokeratosis with parakeratosis, spongiosis and lymphocytic infiltrate in the dermis are revealed. The previously assumed importance of Odland bodies in the pathogenesis of dermatosis is now doubtful. Unlike CD, this dermatosis appears in adolescence and middle age and is characterized by small horny papules that are not prone to plaque formation (27,29,31,32,33).

Actinic keratosis is a skin disease characterized by limited, dense hyperkeratotic lesions in areas exposed to solar radiation. The probability of occurrence of squamous cell carcinoma in lesions of actinic keratosis, according to some data, is estimated from 0.85 to 10% per lesion per year [48,49,50]. As a rule, squamous cell carcinoma that develops in areas of actinic keratosis

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has a favorable course, but in rare cases it can metastasize (15,16,17).

Porokeratosis is a rare group of acquired or hereditary dermatoses characterized by linear or annular plaques with a keratotic border.

Disseminated superficial actinic porokeratosis (DSAP) is a disease characterized by impaired keratinization. Disseminated superficial actinic porokeratosis is one of six types of porokeratosis. It has wider participation than most other options. These other variants include linear porokeratosis, Mibelli porokeratosis, punctate porokeratosis, palmar and plantar disseminated porokeratosis, and disseminated superficial porokeratosis. Other rare variants are ptychotropic porokeratosis, facial porokeratosis, giant porokeratosis, hypertrophic verrucous porokeratosis, reticular porokeratosis, and eruptive pruritic papular porokeratosis. The eruptive form of porokeratosis is associated with malignancy, immunosuppression, and a proinflammatory state. Rashes appear all over the body. A feature that is observed in all these variants is the horn-shaped plate. On histology, it appears as a column of parakeratotic cells and is characterized by a raised ridge bordering the porokeratotic lesions. Risk factors for porokeratosis include genetics, immunosuppression, and ultraviolet light. Lesions in disseminated superficial actinic porokeratosis begin as papules and pink to brown macules with a raised border on exposed skin that may be asymptomatic or mildly itchy. These lesions are considered precancerous. There is a risk of malignant transformation to squamous cell or basal cell carcinoma from 7.5 to 10% (12,22,23)

Eruptive pruritic papular porokeratosis is a rare subtype of porokeratosis that manifests as an acute exacerbation of an annular papule with a distinct peripheral border of a hyperkeratotic ridge and intense itching. EPPP mainly occurs in older East Asian men. Its etiology and pathogenesis are unknown (24).

The development of disseminated superficial porokeratosis is sometimes observed in association with renal transplantation, autoimmune diseases, and various hematologic disorders, suggesting that certain immunosuppression may cause widespread abnormal keratinization. It may also be associated with exacerbation of diabetes mellitus due to the formation of anti-insulin antibodies (32).

Benign lichenoid keratosis (BLK, LPLK) is clinically often misdiagnosed as superficial basal cell carcinoma (BCC), especially when it occurs on the trunk. However, regression of the BCC may be associated with lichenoid interface dermatitis, which may be misinterpreted as BLK on histopathological sections (48).

Benign lichenoid keratosis is a skin lesion consisting of a non-pruritic papule or slightly indurated plaque, histologically characterized by a band-shaped inflammatory infiltrate involving the surface of the skin.

The authors believe that benign lichenoid keratosis may be a specific disease rather than an inflammatory

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stage of regressive solar lentigo, large cell acanthoma, or reticulate seborrheic keratosis (16,17,19).

A study of palmoplantar keratoderma in eighty-two cases showed that the cause of palmoplantar keratoderma is twenty different diseases, both hereditary and acquired. The maximum number of cases occurs in the hereditary variety of palmoplantar keratoderma (Unna-Tost syndrome) (28.05%). While among acquired diseases the leading cause was psoriasis (17.07%). Two histopathological types of Unna-Tost syndrome and their correlation with clinical features have been reported (4,5)

Keratoderma spinosa is a rare dermatosis consisting of multiple projections located on the palms and soles, with a distinct histopathological feature of a parakeratotic column over a hypogranular epidermis. Although there are some hereditary cases, most are acquired. The latter may be idiopathic or associated with neoplasms and chronic systemic diseases (15,25).

In some literature sources, keratoderma spinosum is referred to as keratoderma spinosa. This condition is identified under several names, such as “music box spinal keratosis” and “palmoplantar filiform hyperkeratosis,” which creates ambiguity in the diagnostic and histopathological features of the disease. Because of its association with cancer, all patients with keratoderma spinosa should undergo baseline cancer screening based on age and then once or twice a year or as symptoms appear (3,4).

The incidence of skin malignancies has been increasing over the years (46,47). Since 1960, their incidence worldwide has increased annually by 4–8% and amounts to about 3 million newly identified cases per year. One of the most significant etiological factors is considered to be excessive insolation - frequent exposure to the sun for a long time and repeated sunburn. In many cases, malignant epithelial skin tumors develop in the setting of preexisting dermatoses such as actinic keratosis and Bowen's disease (22).

Bowen's disease is an intraepidermal form of squamous cell carcinoma (or squamous cell carcinoma in situ) in the form of a single, slowly growing plaque. Its development is most often associated with exposure to ultraviolet radiation, less often with skin trauma or contact with arsenic. In this regard, two forms of the disease are considered: one is localized in open areas of the skin (exposed to insolation), and the other is localized in closed areas. The course of Bowen's disease is steadily progressive, although in the vast majority of cases it remains cancer in situ throughout the patient's life. Invasive squamous cell skin cancer develops against the background of Bowen's disease with a frequency of 5% to 11% of cases of long-term existence of the pathology. As long as the disease remains in the intraepidermal stage, metastases do not occur. It is possible to differentiate actinic keratosis and Bowen's disease only on the basis of histological examination. Thus, with actinic

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keratosis, dysplastic changes in the epidermis are observed, which occupy no more than ⅔ of its thickness, sometimes with penetration of epidermal strands into the upper parts of the dermis. However, atypical cells can spread throughout the entire thickness of the epidermis - in such cases they are called bowenoid actinic keratosis (22,24). Bowen's disease is characterized by a sharp thickening of the epidermis, consisting of enlarged cells, in places piling up on each other, with pronounced polymorphism and polychromasia, with acanthotic growths to the reticular layer of the dermis (23,26). Proliferation of atypical keratinocytes, as in bowenoid actinic keratosis, is observed throughout the entire thickness of the epidermis. Actinic keratosis with foci of Bowenization and Bowen's disease are distinguished by dysplastic changes in the keratinocytes of the follicular epithelium - a sign inherent in Bowen's disease. In addition, with bowenoid actinic keratosis, manifestations of solar elastosis are always observed in the dermis. However, according to some authors, the bowenoid type of solar keratosis is histologically indistinguishable from Bowen's disease and at this stage of development is regarded as carcinoma in situ (1,22,6,28). Despite the atypia of keratinocytes, characteristic of both actinic keratosis and Bowen's disease, there are no signs of true invasion - the boundary between the epidermis and dermis remains clear.

Of particular importance in all cases is the study of the expression of a number of cellular markers involved in the mechanisms of development of malignant skin tumors, such as oncoproteins associated with intercellular adhesion and proliferation. Several nuclear and membrane antigens are known, changes in expression of which are due to proliferative activity cells. One of the most studied molecular biomarkers is the indicator of proliferative activity Ki-67, whose antibodies react with proliferating cells. If the cell does not proliferate, this interaction does not occur. Normally, in healthy epidermis, Ki-67 expression is observed only in the basal layer, and the average proliferative index, according to various sources, varies from 0.8 to 11% (24,25,34,35,36).

The architectural integrity of the epidermis is ensured by keratins and intercellular adhesion molecules - epithelial cadherins. E-cadherin is a calcium-dependent adhesion molecule characteristic of epithelial tissue cells. Its long extracellular sections form parallel dimers on the cell surface, which, when in contact with E-cadherin molecules of neighboring keratinocytes, form strong zipper-type bonds. A decrease in intercellular adhesion allows affected cells to split off from normal ones, which leads to destruction of histological structures. Normally, in the epidermis, E-cadherin is detected in 100% of cells in the form of uniform membrane staining. Increased cell proliferative activity and impaired expression of E-

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cadherin indicate an increase in cell invasive capacity (26,27).

Data from a number of authors indicate that actinic keratosis, bowenoid actinic keratosis and Bowen's disease represent different stages of the development of the same malignant process. The predominance of low proliferative activity, the expression of Ki-67 in the lower parts of the epidermis and the preservation of adhesive interactions between cells in actinic keratosis indicate the initial stages of the process and its low invasive potential (22,23).

Epithelial skin tumors are common human neoplasms, accounting for from 20–24.9 to 55.4–61.7% of calls for skin neoplasms. One of the key factors contributing to the activation of proliferative processes in the skin with the subsequent development of neoplasms of various natures is the infection of skin cells with the human papillomavirus (HPV). Certain characteristic HPV fragments suppress the activity of the keratinocyte p53 gene, which leads to uncontrolled proliferation of keratinocytes. The importance of certain types of HPV in the development of a number of skin tumors has been shown (27,47,49).

The PCNA protein is recognized as a more accurate indicator of proliferation, identifying cells in the process of preparing for division in the S-phase of the cell cycle. The evidence that the S-phase in cells affected by HPV is longer (from 18 to 20 hours) than the S-phase in normal epidermal keratinocytes (16 hours) is confirmed by immunohistochemical studies. Seborrheic keratosis is the most common benign skin tumor in different regions of the world (47,49).

It is known that the vast majority of proto-oncogenes and tumor suppressors are components of several common signaling pathways that control the cell cycle, apoptosis, genome integrity, morphogenetic reactions and cell differentiation. Changes in these signaling pathways ultimately lead to the development of tumors. To date, about a hundred potential oncogenes (cellular and viral) and about two dozen tumor suppressors are known. Changes characteristic of predominantly malignant human tumors have been identified, including highly specific anomalies used to make a diagnosis, while almost no attention has been paid to benign formations (16,22).

Two families of proteins, inhibitors of cyclin-dependent kinases, have been identified: Ink4 and Cip/Kip. The first includes four members, including the tumor suppressors p15INK4b and p16INK4a. Ink4 proteins have a fairly narrow specificity: by binding the cyclin-dependent kinase (Cdk) Cdk4 and Cdk6, they prevent the formation of their complexes with cyclins D. The Cip/Kip family consists of three members: p21WAF1/CIP1, p27KIP1a and p57KIP2. These proteins bind and inhibit already fully formed complexes of cyclin D – Cdk4(6), cyclin E – Cdk2 and cyclin A – Cdk2 [5, 6]. Inhibition of the functions of cyclin-dependent kinases leads to hypophosphorylation of the pRB protein, which reduces the expression of E2F-dependent genes, blocks the transition of the cell from

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the G1 phase to the S phase, and controls cell division and proliferation. Many sources confirm that disturbances in the G1 phase and G1/S checkpoint lead to uncontrolled tumor growth. Thus, it has been experimentally proven that a decrease in p16 protein expression leads to hyperphosphorylation of pRB and subsequently leads to activation of the transcription of S-phase-specific genes. The p16 protein was discovered by researchers in 1993 and since its discovery has become one of the most sought-after markers in the field of cancer research [10]. It is encoded by the tumor suppressor gene CDKN2A, located on chromosome 9 (9p21.3). The participation of this gene has been noted in the development of both sporadic and familial forms of melanoma, glioma, lung cancer, T-cell leukemia, and B-cell leukemia. In addition, p16 is currently used as a prognostic biomarker for patients with oropharyngeal squamous cell carcinoma and cervical cancer. The expression of this protein and its role in the pathogenesis of benign skin tumors, in particular seborrheic keratosis, have been little studied (22,24,44,45,49).

Thus, Y. H. Wu et al. in 17 cases of seborrheic keratosis with signs of bowenoid transformation, he found increased expression of p16 and p21 in the cells, which is also characteristic of Bowen's disease and bowenoid papulosis. They were asked to study p16 in patients with seborrheic keratosis to identify possible malignancy of the elements. Other authors - S. Nakamura et al., having identified in skin samples from KS lesions (including in cultured keratinocytes from patients with KS) a pronounced expression of the p16 protein in all tumor cells, associated this not with the possibility of malignancy, but with a violation of the cell cycle , blocking the entry into the S-phase of cells and their premature aging. In support of this hypothesis, in the 4 studied SC samples, genetic analysis revealed the absence of DNA fragmentation in tumor cells, whereas in normal epidermis fragmentation was present in the granular and stratum corneum. This indicates that apoptosis is inhibited in KS. Brueks et al., studying 10 cases of seborrheic keratomas of exclusively acanthotic and irritable types, noted an average level of expression of the p16 protein and a pronounced, diffuse expression of another protein, the p27 kinase inhibitor, which, in his opinion, indicates the dominant influence of this protein on cell proliferative activity. Like p16, the p27 protein (Kip1) regulates the course of the cell cycle and is responsible for its arrest in the G1 phase. It is the product of the human CDKN1B gene (22,43).

So, today, ideas about the role of proteins - inhibitors of cyclin-dependent kinases in oncogenesis are not entirely clear; the data from most studies are contradictory. The possibility of using them in practice as prognostic biomarkers opens up prospects for an individual approach to the treatment of each patient, understanding the pathogenesis of many both malignant and benign human tumors, which

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determines the relevance and need for their further study.

CONCLUSIONS

Studying the morphological and genetic different types of keratoses is key for correct diagnosis and choice of treatment. The association between metabolic disorders and skin diseases highlights the need for an integrated approach to the management of patients with chronic diseases, including diabetes mellitus. Further research is needed to better understand the pathogenesis and develop effective treatments.

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