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Premalignancies and intraepithelial neoplasms of the skin – an update

Stany przedrakowe i raki przedinwazyjne skóry – ostatnie doniesienia

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Summary

The process of skin carcinogenesis involves a series of transitional events, which can be initiated and promoted by many events such as exposure to physical or chemical carcinogens, chronic inflammation and viral infection.

Precancerous skin lesions and carcinomas *in situ* of the skin represent the early stages of epithelial skin tumors. Clinical observations, histological analysis, as well as molecular and cytogenetic studies have shown actinic keratoses and Bowen's disease to be precursors of squamous cell carcinomas. The presence of arsenical keratoses, tar-induced dermatosis and X-ray irradiation-related keratosis may be associated with basal and/or squamous cell skin cancers. Other intraepithelial neoplasms include mammary and extramammary Paget's disease. Anogenital HPV can cause intraepithelial vulvar, penile and anal intraepithelial neoplasias, each named for the affected site: AIN (anal intraepithelial neoplasia), PIN (penile intraepithelial neoplasia), and VIN (vulvar intraepithelial neoplasia).

This article provides an update on the diagnosis and management on these premalignant conditions.

Streszczenie

Proces karcinogenezy w obrębie skóry obejmuje szereg etapów, które mogą być inicjowane i stymulowane przez różne czynniki fizyczne i chemiczne, przewlekłe zapalenie oraz infekcje wirusowe.

Stany przedrakowe i raki *in situ* skóry stanowią wczesne stadium nowotworów nabłonkowych skóry. Obserwacje kliniczne, obraz histopatologiczny, jak również badania molekularne oraz cytogenetyczne wykazały, że rogowacenie słoneczne i choroba Bowena poprzedzają rozwój raków kolczystokomórkowych skóry. Rogowacenie arsenowe, smołowcowe i uwarunkowane promieniowaniem X mogą być związane z występowaniem raków podstawno- i/lub kolczystokórkowych skóry. Inne raki przedinwazyjne skóry to choroba Pageta brodawki sutkowej i pozasutkowa choroba Pageta. Infekcje wirusem brodawczaka ludzkiego (*Human Papilloma Virus* – HPV) okolic narządów płciowych i odbytu przyczyniają się do rozwoju raków przedinwazyjnych sromu, prącia i odbytu, określanych w zależności od lokalizacji śródnabłonkową neoplazją sromu (*vulvar intraepithelial neoplasia* – VIN), prącia (*penile intraepithelial neoplasia* – PIN), odbytu (*anal intraepithelial neoplasia* – AIN).

W artykule przedstawiono ostatnie doniesienia dotyczące stanów poprzedzających rozwój raków skóry z uwzględnieniem diagnostyki i terapii.

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INTRODUCTION

The process of skin carcinogenesis involves a series of transitional events, which can be initiated and promoted by many events such as exposure to physical or chemical carcinogens, chronic inflammation and viral infection. The primary factor contributing to the molecular pathogenesis of non-melanoma skin cancers (NMSC) is unprotected skin exposure to ultraviolet (UV) radiation. While UV-A (320-400 nm) induced photo-oxidative stress indirectly induces characteristic DNA mutations, the spectrum of UV-B (290-320 nm) irradiation directly results in the formation of cyclobutane (thymin) dimer formation in DNA and RNA (1). Many tumour suppressor genes and oncogenes have been studied and implicated in photocarcinogenesis, particularly p53, PTCH1, BRM and RAS (2). Persistent HPV infection is confirmed necessary factor for development of cervical cancer and anogenital neoplasia. The most common high-risk HPV types observed in anogenital intraepithelial neoplasia or anogenital cancer are HPV

16, 18 and 45 (3). Rates of anal HPV infection are extremely high in HIV-positive patients, particularly in men who have sex with men (MSM) (4). HPVs infect stratified epithelia and link productive replication with differentiation. The viral oncoproteins E6, E7 and E5 play a key role in the (pre)malignant transformation (5). Occupational skin cancers have particularly been due to industrial exposure to chemical carcinogens such as polycyclic hydrocarbons (e.g. from coal tar products) or to arsenic (6). Ionizing radiation such as X-rays can also cause skin cancer (5).

This article provides an update on precancerous lesions and carcinomas *in situ* of the skin and anogenital region with special emphasis on the diagnosis and management.

ACTINIC KERATOSIS

Actinic keratosis (AK) is the most common precancerous lesion of the epidermis. Clinically, they can vary from small erythematous scaly macules to pigmented rough patches in sun-exposed areas. The field cancerization can contain multiple clinically visible AKs, subclinical AKs (only visible under a microscope), and groups of keratinocytes with genetic mutations detectable only with molecular biology methods (7). AKs are characterized by keratinocytic atypia and considered carcinomas *in situ*. Three histologic grades of AK can be distinguished on the basis of degree of intraepidermal involvement of keratinocytic atypia: AK-I, in the lower third of the epidermis; AK-II, in the lower two-thirds of the epidermis; and AK-III, affecting the full thickness of the epidermis (8). Chronic exposure to ultraviolet radiation in fair-skinned patients is the most important risk factor for the development of AK. In the absence of appropriate repair mechanisms, these DNA changes represent the initiation of keratinocyte mutations which can progress into the development of AKs (9). Associated factors include advanced age, male sex, outdoor occupations (e.g., farming or seagoing occupations) and recreational activities (e.g., tennis, golf), place of residence (high altitude, latitudes closer to the equator), and exposure to artificial UV radiation (10). Skin phototype (I and II), chronic iatrogenic immunodeficiency (e.g., in organ transplant patients), genetic syndromes that undermine DNA repair mechanisms or chromosome stability, photosensitivity and exposure to certain toxins or drugs that affect the cell cycle (e.g., hydroxyurea or arsenic, and various biologic agents used in oncology are also probably implicated) (10). The relative risk of AK is 250-fold higher in transplanted patients than in immunocompetent individuals (11). Sunscreen has shown to be an effective AK prevention method reducing up to 24% AK lesions over time (12). Research also has shown the benefits of oral Nicotinamide use (500 mg daily or twice daily for 4 months) that caused 29-35% relative reduction in AK count (13). Products that combine sun screens with DNA reparative agents are currently being tested (14). Diagnosis of AK is mainly clinical. Hypertrophic or hyperkeratotic, pigmented, lichenoid and atrophic variants are recognized. Dermoscopy can help distinguish AK from superficial basal cell carcinoma, lentigo maligna or pigmented basal cell carcinoma. Confocal scanning laser microscopy and photodynamic diagnosis is currently used more for research than routine clinical care. AK lesions may regress spontaneously, remain AKs, or progress to invasive SCC (11). The risk of progression to invasive SCC over 10 years is between 6.1 and 10.2% and rises to 40% in immunodeficient patients (15). The progression to invasive disease should be suspected when a lesion appears inflamed, indurated, ulcerated or large (> 2 cm). Other signs of possible progression are bleeding, rapid growth, lack of response to appropriate treatment, or recurrence after successful treatment.

The choice of treatment should depend on patient profile, lesion characteristics, what options are locally available, and other constraints at the time of treatment. When lesions are few and isolated, treatment should target individual lesions. The most commonly used therapy for AK treatment is cryotherapy with liquid nitrogen. Side effects include blistering, hypopigmentation, hyperpigmentation, scarring, and infection as well as discomfort during the freezing cycle. Targeting options of AK treatment include also electrodessication and curettage. Curettage harvests tissue for pathology, although it is impossible to confirm whether there is tumor invasion of the margins. Surgical removal of an AK is not routine and is undertaken only when there is suspicion of invasive SCC or lesions are recurrent (10, 15). In the management of multiple actinic keratoses, field therapies should be preferred to more destructive and/or invasive treatments, which allows treatment of both visible and subclinical lesions (16). Field therapies can be divided into patient-administered options such as topical therapies and physician-administered options such as photodynamic therapy (PDT), laser resurfacing, dermabrasion, and medium – to deep-depth chemical peels. Current approved topical therapies include 5-fluorouracil (5-FU) 0.5-5% cream, imiquimod 5% and 3.75%, diclofenac sodium gel 3%, and ingenol 0.015% and 0.05% gel (17). All of the topical agents are associated with common side effects that include localized erythema, flaking, scaling, and crusting; however, dyspigmentation and scarring occur infrequently (18). It is noteworthy that the uniquely brief regimen for ingenol mebutate, 2 to 3 days, produced clearance rates similar to those with the other agents, which have treatment regimens of several weeks (18). Combining destructive treatments and topical ones may be advisable when there is progression to invasive SCC. Topical treatment with PDT and imiquimod may also be a beneficial combination (10). Oral systemic retinoids, dermabrasion, chemical peeling, and laser therapy are considered second-line or coadjuvant treatments and they should be considered for possible use in special circumstances (10).

ACTINIC CHEILITIS

Actinic cheilitis (AC) is basically AK of the lower lip (in 95% of the cases), and it is caused by chronic and excessive exposure of the lips to the ultraviolet radiation in sunlight. AC clinically presents as loss of the usually sharp border of the lip, atrophy of the vermilion border and darkening of the lip at the border between the lip and the skin of the face, as well as ulcers of the lip. Prevalences of AC range from 0.45 to 2.4% of the population (19). The most important risk factors for AC are outdoor activity and skin type (19). Histopathologically, AC is characterized by hyperplasia, acanthosis or atrophy of the epithelium, thickening of the keratin layer, and/or dysplasia, which may range from mild to severe. In connective tissue, basophilic degeneration of collagen fibers, called solar elastosis, is usually detected (19). Dermoscopy is a useful tool for evaluating AC. Dermoscopic characteristics of AC are ill-demarcated borders and vascular telangiectasia, white-coloured projections and island-like structures around the ulcerous areas (20). AC deserves special attention because of its malignant potential to develop into invasive SCC of the lip. The frequency of malignant transformation of these lesions ranges from 10 to 30% (19). Once SCC develops on the lip, the risk of invasion and metastasis to the cervical lymph nodes is higher than that for SCC of the skin.

CUTANEOUS HORN

The cutaneous horn (CH) is defined as a tumour, usually of conical appearance which prevails over the length of its diameter, with large hyperkeratosis in its extreme. Various skin diseases may present with cutaneous horns including viral warts, AK, keratoacanthoma, seborrhoeic keratosis, pyogenic granuloma, discoid lupus erythematosus, verruca vulgaris, Bowen's disease, basal cell carcinoma and squamous cell carcinoma (21). Over 60% of the lesions are benign, 23% of the cases premalignant and 16% of the cases malignant (21). Majority of the cases occur on areas that are exposed to sunlight. Forearm, cartilaginous portion of the ear, leg, and back of the hands may also be involved (22). The incidence of penile CH is particularly low (23). Cutaneous horns should be completely excised and sent for pathological evaluation.

ARSENICAL KERATOSES

Arsenic exposure is a major public health problem affecting very large populations in Bangladesh, West Bengal, Chile, Argentina, Taiwan, the United States, and many other countries worldwide that have or have had elevated levels of arsenic in their water (24). A fraction of chronically exposed populations, usually within a few years of exposure, presents with classic arsenical skin lesions, characterized by hyperpigmentation of the skin with or without palmoplantar hyperkeratosis (25). The presence of these skin lesions is also associated with basal and squamous cell skin cancers (26). Hsu et al. (27) reported that arsenical skin lesions are predictive of internal cancers among Taiwanese decades after the cessation of exposure, specifically lung and urothelial cancers. Arsenic is also believed to be associated with the risk of cardiovascular, respiratory and neurological diseases (28). Nevertheless, arsenicosis from medications containing arsenic, especially those prescribed in alternative systems of medicine, such as Ayurveda and homeopathy, is gradually becoming a possible serious threat to public health, largely because of the unregulated and nonstandardized use of widely available over-the-counter products, without the guidance and supervision of experts in these fields (29).

TAR-INDUCED DERMATOSIS

Skin carcinomas have been recognized as an occupational disease in the acquisition of tar, pitch and mineral oil for a long time. Tar-induced skin lesions are still of importance nowadays, which is reflected in the incidence of new cases and in the relapses of skin tumors (premalignant nonmelanoma skin tumors, SCC, basal cell carcinomas, keratoacanthomas) (30). The frequent irritation and characteristic changes of skin affected by tar were termed "tar itch". The distribution of these skin lesions partly indicates the relevance of sunlight on their pathogenesis. Coal tar ointments are used as treatment of various skin diseases, especially psoriasis and eczema. Several studies have therefore investigated the risk of skin cancer after coal tar treatment but most studies, except one of Stern et al. (31) did not observe an increased risk. According to Roelofzen et al. (32) there is no reason for safety concerns with respect to the risk of bladder cancer after the use of coal tar preparations in dermatological practice. However, the workers should be kept under regular medical surveillance even after having left the tar industry because of the long latency of skin tumors. All warts should be excised and histologically examined, since their removal may prevent the development of cancer.

X-RAY IRRADIATION-RELATED KERATOSIS

Human evidence that ionizing radiation is carcinogenic first came from reports of chronic radiation dermatitis and later skin cancer suffered by people using X-rays in their occupation, including X-ray tube manufacturers, physicians, and engineers. NMSC has been observed in several radiation-exposed groups, including individuals treated with x rays in childhood for tinea capitis or for thymic enlargement. In nearly all of the patients with radiation-induced skin cancer, concomitant radiodermatitis is present. X-ray related cancer has a long latent period. Multiple tumors are frequent as is recurrence in x-ray malignancy (33). Karagas et al. (34) investigated the relative risks of BCC and SCC associated with previous radiation therapy and evaluated these risks in relation to age and time since initial treatment and the medical condition for which radiation therapy was given. Their data suggest that exposure

to therapeutic radiation is associated with BCC but not with SCC. There is evidence that the risk of skin cancer may be higher among those who received radiation therapy at an earlier age. Skin carcinogenicity that is related to the use of X-rays is a concern because of the immunosuppressive effects of the treatment, and this may increase sensitivity to solar radiation (35). Wolfe et al. (36) reported seven cases with a relation between electron beam radiotherapy on sun exposed skin and development of secondary cutaneous tumours.

BOWEN'S DISEASE

Bowen's disease (BD) is a form of *in situ* SCC that clinically appears as a long-standing, oval, erythematous and scaling plaque. Less common variants include pigmented, subungual, periungual, palmar, genital, perianal and verrucous SCC *in situ* (37). Although BD is usually solitary, multiple lesions may occur in10-20% of patients (38). The peak incidence of the disease is in the seventies (39). About 75% of patients have lesions on the lower legs (39). The presence of various types of human papilloma virus have been found in extragenital BD including the oncogenic type 16 (39). Immunosuppression is a risk factor for BD (38). If untreated, 3 to 26% of cases may develop invasive SCC (16). Westers-Attema et al. (40) recommend that a safety margin of 5 mm should be used in treating BD patients to reach a high complete excision rate. Their data show that a hypothetical reduction of the safety margin from 5 mm to 4 or 3 mm decreases the complete excision rate from 94.4 to 87% and 74.1%, respectively.

PAGET'S DISEASE

Mammary Paget's disease is a rare form of breast neoplasm that often presents with a pruritic eczema-like rash involving the nipple-areolar complex. In the United States, 82 to 87% of Paget disease cases include underlying ductal carcinoma *in situ* or invasive ductal carcinoma, but breast masses are palpable in only 14 to 44% of cases (41). The disease is associated with approximately 3% of all breast cancers (42). Most often Paget's disease is diagnosed in women in the sixth and seventh decade with a mean age of diagnosis reported at 62.6 years (43). In any patient presenting with an itching or ulcerated lesion of the nipple, a tissue biopsy should be obtained to exclude the diagnosis of Paget's disease. Histopathologically Paget's disease is characterized by epidermal invasion by malignant glandular cells, which are large, foamy cells that may contain mucin (44). Polarized dermoscopy is a versatile optical tool, easy to use, practical and that can help in early diagnosis of mammary Paget's disease (the presence of bright white streaks structures called chrysalis-like structures) and their clinical and histopathologic correlation (45). As Paget's disease is often associated with malignancy that could be multicentric (defined as two or more foci in separate anatomical quadrants of the breast) or multifocal (multiple foci of carcinoma found in the same quadrant), mammography often is not sufficient and MRI may be necessary to evaluate the true extent of the disease (42). Surgical excision is the recommended treatment (modified radical mastectomy with lymphadenectomy), but recently studies have shown that breast-conserving surgery found no significant differences in terms of overall or disease-free survival (42).

Extramammary Paget's disease (EMPD) is an uncommon intraepidermal adenocarcinoma that arises in areas rich in apocrine glands and involves primarily the epidermis but occasionally extends into the underlying dermis. CK7, CK19, and C-erb B2 are favorable immunohistochemical markers for the diagnosis of EMPD (46, 47). The most common sites of EMPD are the vulvar and anogenital regions, followed by axillae, penoscrotal region, eyelids, umbilicus, and groin (48).

There is a range of interventions from surgical to non-invasive techniques or treatments. The challenges of interventions are to remove or treat disease that may not be visible, without overtreatment and with minimisation of morbidity from radical surgery. Some authors have suggested nonsurgical treatment first, such intralesional interferon or topical imiquimod (49, 50). Yasar et al. (51) suggested radiotherapy to control locally the disease for selected cases. Alternative treatments are photodynamic therapy, laser therapy or chemotherapy (52). Long-term follow-up of patients with EMPD is important because of the possibility of recurrence or development of an associated cancer (53).

BOWENOID PAPULOSIS

Bowenoid papulosis (BP) is an uncommon squamous intraepithelial neoplasia, which manifests as an eruption of flesh colored or hyperpigmented verrucous papules that may become confluent plaques, involving the genitalia and anogenital regions. However, they may also occur elsewhere (54). BP is an infectious disease caused by human papillomavirus (HPV). HPV-16 is the most common causative agent. Some authors (55) reported patients with human immunodeficiency virus infection, which seem to indicate a relation between BP and an immunocompromised status. Histologically, BP is characterised by acanthosis with full-thickness dysplasia, making it challenging to distinguish from other variants of squamous carcinoma *in situ*. The course of BP is variable, ranging from spontaneous regression to progression to chronic disease with the risk of malignancy reported to be at 1% (56).

VULVAR, PENILE AND ANAL INTRAEPITHELIAL NEOPLASIA/SQUAMOUS INTRAEPITHELIAL LESION

The term "vulvar intraepithelial neoplasia" (VIN) was endorsed by the International Society for the Study of Vulvar Disease (ISSVD) in 1986 to describe intraepithelial neoplastic proliferations of the vulvar epidermis (57). **VIN shows morphological characteristics similar to all HPV-associated intraepithe-**

lial lesions such as cervical intraepithelial neoplasia (CIN), anal intraepithelial neoplasia (AIN), vaginal intraepithelial neoplasia (VaIN), and penile intraepithelial neoplasia (58). Previously, other terms had been used to describe histologically similar lesions: "Bowen's disease," "erythroplasia of Queyrat," "bowenoid papulosis," and "bowenoid dysplasia". Currently, the term "squamous intraepithelial lesion" is favored over "intraepithelial neoplasia" (59). The incidence of HPV-associated VIN has been increasing over the past 20 years, especially in women of reproductive age, with the highest frequency reported in women of 20-35 years old (57). The lesions are frequently multifocal, flat, raised, or eroded, white, grey, red, or brown, and asymptomatic in about 50% of cases. Some cases may be accompanied by itching, pruritus, pain, and dyspareunia. They can clinically resemble the other benign dermatoses involving the penis. Histopathologic examination must be performed for differential diagnosis. Based on the architecture and appearance of the intraepithelial lesions VIN is divided into warty (a striking papillary pattern, acanthosis, with cytological signs of viral infection) and basaloid (a flat surface, small atypical parabasal type cells on nearly whole thickness of the epidermis) types (57). A rare variant is "pagetoid VIN" where atypical squamous cells present a pale cytoplasm and are isolated or grouped in small clusters (57). VIN was graded in 3 grades (WHO terminology (60), based on the level of involvement of the thickness of the epithelium by the dysplastic cells: (i) low-grade (VIN 1) if the dysplastic cells involve the lower third of the epithelium; (ii) moderate grade (VIN 2) when the dysplastic cells are present in the lower two-thirds of the epithelium; (iii) high-grade (VIN 3) if there is full-thickness involvement of the epithelium by the dysplastic cells. VIN 3 is synonymous with carcinoma *in situ*. VIN 2 and VIN 3 confer the same risk and rate of progression to invasive carcinoma if untreated (57). Therefore, a 2-tier classification, of "high grade (HSIL)" or "low grade (LSIL)", is favored currently over a 3-tier classification (59). The rate of progression to invasive vulval cancer in women with untreated high-grade VIN is suggested a rate as high as 9%, whereas the risk of progression in treated lesions over a period of years has been reported as between 2 and 5% (61). VIN usually gives rise to basaloid or warty SCC (40% of cases) (62). A retrospective chart review revealed that progression of VIN to carcinoma was accelerated and increased in immune-compromised patients (63). There were no clinical characteristics that formed prognostic factors in VIN, except for multifocality of lesions, which was correlated with a higher recurrence rate (63). High-grade and low-grade vulvar intraepithelial neoplasias appear to be associated with localized amyloidosis of the vulva (64). Vulvar HPV infection is responsible for the development of most of the vulvar (pre)neoplastic lesions, except for the "differentiated" (simplex) type of VIN which is associated with vulvar dermatoses, especially the lichen sclerosus and lichen simplex chronicus (57). The latter is the precursor lesion of the most common type of squamous cell carcinoma (SCC) in the vulva, namely keratinizing SCC (representing 60% of cases). dVIN type and non-HPV-related vulvar SCC occur commonly in elderly women (57). Usual VIN driven by high-risk HPV infections is characterized with a positive p16 immunohistochemistry and a high Ki-67 proliferation index (62). In contrast, differentiated or simplex-type VIN is consistently negative for p16 and the majority of the cases harbour TP53 mutations, correlating with p53 positivity by immunohistochemistry (62). In last decade a new diagnostic techniques were introduced: liquid-based cytology and HPV DNA testing (3).

The treatment of VIN depends on its grade and location on the vulva. VIN 2/3 lesions are considered to have a high propensity for malignant conversion; hence, they are either excised or ablated. Carbon dioxide (CO_2) laser vaporization (a type of ablation) and surgical excision are the most popular treatment modalities included. Ultrasonic surgical aspiration is another surgical technique which involves the use of a high frequency ultrasonic vibrator which destroys tissue by cavitation. This system allows precise and selective tissue dissection. Argon beam coagulation is comparable to other vulva organ conserving therapies (66). Repeat treatments are also possible, which is important in a condition such as VIN, which tends to be multifocal and recurrent (66). Recently, less-invasive modalities have been developed, such as photodynamic therapy and the topical use of immune modulators. One trial that is currently recruiting participants with the aim of comparing primary imiquimod therapy with surgical excision will report results in 2016 (PITVIN 2013) (61). Systematic review performed by Couto et al. (67) showed that there is a protective effect of HPV vaccination against CIN2+ lesions associated with the HPV types included in HPV vaccines, all VIN2+ and VaIN2+, and condyloma acuminate (HPV related and not).

In situ penile carcinomas are usually regarded as uncommon disorders but probably are underreported. The precursor to penile SCC, PIN, is clearly associated with HPV. Important predisposing factors of penile SSC are lack of circumcision and penile lichen sclerosus (65). AIN is the precursor lesion to anal SCC. AIN and anal cancer are some of the most important and most common HPV related skin diseases affecting HIV patients. Anal cancer is more common than either vulvar or penile carcinoma. PIN and penile cancer, as well as for AIN and anal cancer, recommendations for treatment are not well established. Surgery remains the mainstay of treatment for all of these conditions, however, in some cases, early lesions may be treated with topical therapies including with podophyllin, 5-fluorouracil, or imiquimod (68).

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