Coexistence of Segmental Multiple Keratoacanthoma, Hidradenitis Suppurativa and Multiple Sclerosis

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ABSTRACT

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The purpose of this study is to present a consistent treatment of a patient who developed recurrent multiple keratoacanthomas within a linear epidermal nevus. The unusual nature of keratoacanthoma lies in its tendency for spontaneous regression [1]. Additionally, our patient was diagnosed with multiple sclerosis and treated with dimethyl fumarate. He also developed hidradenitis suppurativa during dimethyl fumarate therapy. The paper presents the patient's therapy with a focus on the use of systemic retinoids.

Keywords: *keratoacanthoma, hidradenitis suppurativa, fumarates, systemic retinoid, multiple sclerosis*

STRESZCZENIE

Współwystępowanie segmentalnych mnogich rogowiaków kolczystokomórkowych, trądziku odwróconego oraz stwardnienia rozsianego

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Celem pracy jest przedstawienie spójnego leczenia pacjenta, u którego w obrębie linijnego znamienia naskórkowego wykształciły się, nawracające, mnogie, rogowiaki kolczystokomórkowe. Jest to szczególna postać nowotworu, a nietypowość zawdzięcza tendencji do samoistnej regresji [1]. U naszego pacjenta dodatkowo zdiagnozowano stwardnienie rozsiane, leczone fumaranem dimetylu. Pacjent podczas terapii fumaranem dimetylu rozwinął trądzik odwrócony. W pracy przedstawione jest leczenie pacjenta, ze zwróceniem uwagi, na wykorzystanie ogólnie podawanych retinoidów.

Słowa kluczowe: *rogowiak kolczystokomórkowy, trądzik odwrócony, fumarany, systemowe retinoidy, stwardnienie rozsiane*

Case report

A 35-year-old Caucasian male was referred to our clinic with a linear epidermal nevus on the upper left extremity. It stretched from the sternal region, over the shoulder, down the elbow and forearm on the other side , to the patient's palm (Fig. 1). The epidermal nevus appeared two weeks after his birth and reports no redness or itching of the nevus. At that time, the patient was otherwise healthy, with a moderate overweight status of 75 kg, BMI 27.55. He had been a smoker since adulthood (25.5 pack-years). Multiple crateriform lesions of 3-24 mm in diameter started to appear at the age of 22 within the epidermal nevus. Diagnosis of keratoacanthoma (KA) was confirmed after deep curettage of the lesion and histopathological examination. Various treatment modalities were used for multiple and newly appearing KAs, including surgical excision, intralesional methotrexate at a dose of 2 ml for each lesion larger than 10 mm, and curettage or CO2 laser for smaller ones. KAs appeared especially in sun-exposed ar-

eas of the body. Minor injuries also accelerated the growth of KA lesions.

At the age of 36, he was diagnosed with early demyelinating, active, mild multiple sclerosis. Laboratory tests showed leukocytosis and hematuria with no apparent cause. Magnetic resonance imaging (MRI) revealed several active lesions in the brain and spinal cord. Treatment with dimethyl fumarate was implemented at a dosage of 240 mg twice daily. No changes in the dynamic of new KA appearances were noted during the treatment. At the age of 38, the patient developed mild hidradenitis suppurativa (HS) in the axilla and groins. This was treated topically with 3% benzoyl peroxide/1% clindamycin gel and three-month courses of oral lymecycline, 300 mg per day, followed by oral isotretinoin, 20 mg per day. This treatment provided good control of the disease. At the same time, HS involving the groin area was diagnosed in the patient's son.

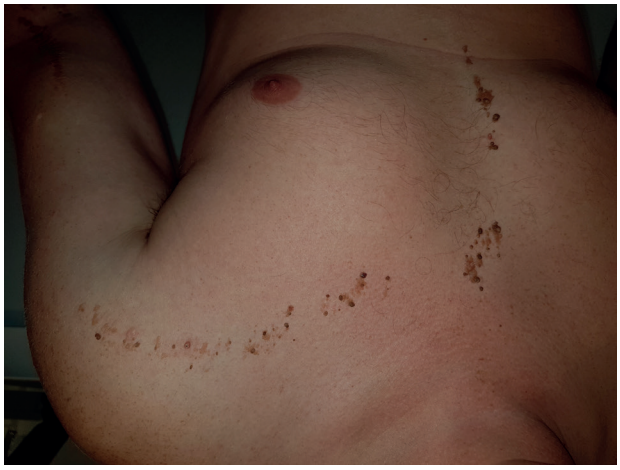
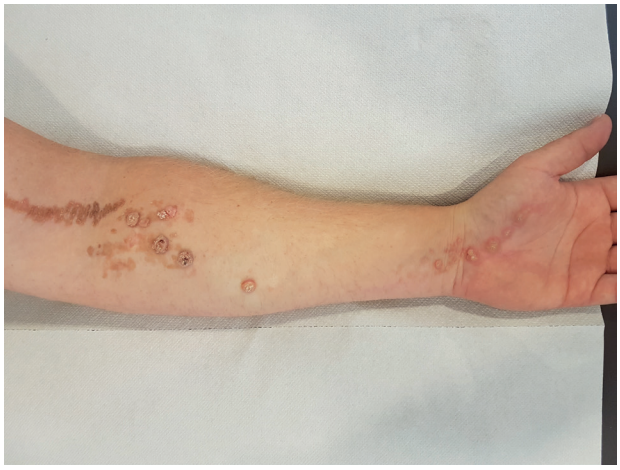


Figure 1. Epidermal nevus following Blaschko's lines – sternal, subclavicular, and along the anterior arm, cubital fossa, flexor surface of the forearm, and palm



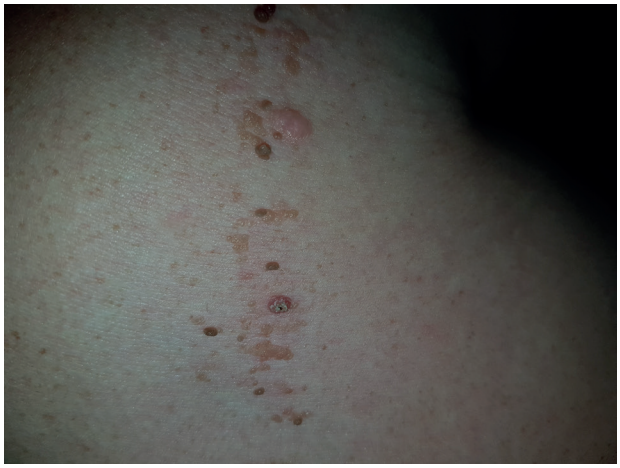


Figure 2. KA developing with the epidermal nevus. The clinical picture of KA usually takes the form of nodules with a crater-like depression filled with keratin masses in the center of the lesion

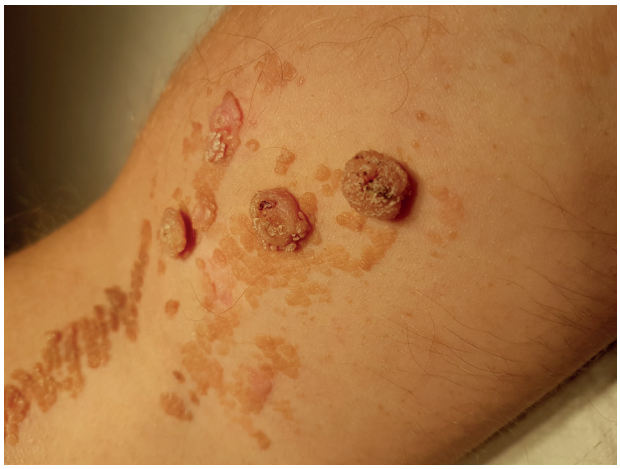


Figure 3. Some KAs raised within traumatized, previously treated, or more verrucous parts of nevi had a less regular verrucous or cauliflower appearance

Discussion

The epidermal nevus follows the Blaschko lines, which represent the embryological development of mosaic skin [2]. In keratinocytic epidermal nevi, mutations in the fibroblast growth factor receptor 3 (FGFR3) gene have been detected in about 30% of patients [2]. Epidermal nevi can be divided into non-organoid keratinocytic nevi and organoid nevi, which include the syndrome of sebaceous linear nevi (NS) and nevus comedonicus [3]. The etiology of NS is not fully understood, but recent research suggests a connection with postzygotic somatic mutations associated with the HRAS, NRAS, and KRAS genes [4]. Malignancies may develop within NS and one of the most common

is KA [4]. Keratoacanthoma can manifest in various forms depending on its location, appearance, and clinical behavior. Examples include KA centrifugum, Giant KA, Subungual KA, Intraoral and other mucous membrane KA, Generalized eruptive KAs of Grzybowski, and Multiple KAs of Ferguson-Smith type [1]. The exact origin of KA is uncertain, but several factors are believed to contribute to its development. These include sun exposure, as evidenced by the presence of keratoacanthomas in patients with xeroderma pigmentosum [1]. Other contributing factors include chemical tumorigenesis, viral infections, and trauma, which may increase the incidence of KA due to their more frequent occurrence at scars and near skin graft sites [1].

Multiple KAs are sporadic or familial in an inherited autosomal dominant variant of Ferguson-Smith type [1]. A mutation in transforming growth factor beta receptor 1 is specific to the Ferguson-Smith KA type [1]. We did not perform genetic studies for mutations in either the epidermal nevus or the keratoacanthoma in our patient.

A solitary KA should be excised surgically whenever possible or feasible. Other treatment options include curettage, laser therapy, electrodesiccation, cryosurgery, radiation therapy, photodynamic therapy, topical treatment with 5-fluorouracil, imiquimod, podophyllin, and intralesional administration of methotrexate [1].

Many cell cycle regulatory pathways are involved in the pathogenesis of KA, including the Wnt pathway. Wnt is activated during growth and deactivated in the regression phase [1]. Retinoids reverse Wnt-related KA proliferation, leading to tumor regression [1]. Therefore, retinoid treatment may be valid, especially for multiple KAs [1]. The dose of acitretin ranges from 0.5 to 1.0 mg/kg/day at the beginning of treatment and may be reduced if necessary [1]. Our patient started taking isotretinoin, beginning with a dose of 20 mg, only after HS had been diagnosed. Isotretinoin has been used to treat KA with satisfying results since 1984 with a dosage of 1-2 mg/kg/day [5,6].

Genetic factors play a role in the etiopathogenesis of HS, involving various heterozygous mutations in subunits of gamma-secretase [7]. HS deviates from the typical infectious disease profile by lacking a singular bacterial agent and instead displaying a diverse bacterial flora. This chronic condition may exhibit periodic acute flares or persist without them [7]. Other factors influencing HS include obesity, smoking, mechanical stress, and rheumatologic diseases [7].

Systemic retinoids can be used in HS both as anti-inflammatory drugs and as a means to normalize keratinization of affected glands. The retinoids reduce inflammation of the dermis and epidermis by inhibiting cell chemotaxis and the release of pro-inflammatory mediators through neutrophils, for example, inhibiting IL-6 synthesis [7]. Acitretin can influence the growth cycle of skin cells, helping regulate cell differentiation and thinning the cornified layer by reducing the proliferation rate of keratinocytes [7]. In the study referenced, patients treated with acitretin received doses ranging from 0.25 to 0.88 mg/kg, while doses of etretinate ranged from 0.35 to 1.1 mg/kg [7]. In our patient, after using isotretinoin, we noticed a marked improvement in the HS lesions under the armpits. However, we are now considering increasing the dose to gain a better effect on KA or switching to acitretin. According to the literature, acitretin seems to potentially have favorable efficacy for both multiple KA and HS.

The coexistence of multiple sclerosis (MS) and KA appears to be coincidental. The pathological mechanism of MS has not been fully understood yet. The etiopathogenesis describes complex relationships between genetic predispositions, environmental factors such as viral infections and vitamin D deficiency, and autoimmune mechanisms targeting the central nervous system. Immunomodulatory drugs are one of the options to treat MS. Our patient was taking dimethyl fumarate (DMF), an anti-inflammatory and immunomodulatory drug registered for MS and psoriasis. There have been reports of its usage in other inflammatory diseases, including HS [8,9,10]. The HS started when our patient had already been treated with DMF, but the course of the disease was mild. DMF is an immunosuppressive drug and could potentially increase the appearance of KA [1,11]. However, we did not notice an increase in the number of new KAs in our patient after initiating treatment with DMF.

Treating a patient with several comorbidities is challenging, and careful selection of the drugs used is necessary. The goal is to find drugs that could potentially improve more than one disease while avoiding or carefully monitoring treatments that could worsen another condition, as was the case with our patient, where immunosuppression could facilitate tumor progression.

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All authors declare no conflict of interest.

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