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Abstract.

The pathogenesis of skin cancer remains shrouded in mystery. Nevertheless, a substantial amount of new data is now available to provide a logical explanation regarding the possible link between 1) the occurrence of single or multiple acquired/somatic mutations and 2) the generation and progression of skin cancer, as well as 3) the potential association of the above two facts with the availability of nitrosamines in drugs for hypertension, diabetes, gastritis, acne, tuberculosis, various other antibiotics, etc.

The nitrosogenesis of skin cancer is slowly but surely being established as a significant concept that cannot be ignored for longer periods of time. It should only be analysed in detail with a view to future prevention for the benefit of public health.

Although this information has been known for decades (but in relation to the development of other cancers), there is still no comparative analysis of the mutations that occur after ingestion of a particular mutagen, also known as nitrosamine. This analysis could highlight/support or reject to some extent the thesis of the role of nitrosamines and genetic instability leading to the subsequent generation of a malignant cell clone.

The notion of skin cancer nitrosogenesis should become a priority concept very soon, but it should also become an evidential memory, a byword, and an equivalent of the ignorance with which modern civilization has treated its own health for decades within the processes of globalization. It is these processes that include nitrosamines as a major component of the “medicinal and nutritional menu” of patients.

It remains unclear at present why regulatory authorities are making endless attempts to legalise the availability of a number of mutagens/human carcinogens in the most commonly distributed medicines worldwide. And to persuade “others” that there is no risk from their permanent, controlled and long-term intake.

We present a patient who had been taking 2 sartans (valsartan/olmesartan) over the years as monotherapy and in combination with hydrochlorothiazide, who developed over time and could also contribute to some extent to the progression of an already present tumour branch, but this influence is rather minor and without significant clinical relevance.

Skin cancer could be seen in the near future precisely as a model of a side reaction after application or long-term contact with mutagens called nitrosamines.

Based on the above, and wishing to add to the worldwide data on the heterogeneous cancers that occur after contact with nitrosamines, we draw the attention of the scientific community to the risk of developing keratinocytic cancer after intake of nitrosamine-contaminated drugs: sartans and thiazide diuretics. We believe that the role of the generic substance in these drugs could also contribute to some extent to the progression of an already present tumour branch, but this influence is rather minor and without significant clinical relevance.

We present a patient who had been taking 2 sartans (valsartan/olmesartan) over the years as monotherapy and in combination with hydrochlorothiazide, who developed over time and within this intake two forms of keratinocytic cancer: verrucous carcinoma and basal cell carcinoma. The focus of discussion concerns a newly introduced medical concept: nitrosogenesis of skin cancer. The detailed study of nitrosogenesis should be a major, primary task for regulators, researchers, clinicians, and
pharmaceutical companies.

**Key words.** Nitrosamines, olmesartan, valsartan, irbesartan, hydrochlorothiazide, basal cell carcinoma, verrucous carcinoma.

**Introduction.**

Keratinocytic tumors have been described repeatedly in the world literature as a possible side effect of treatment with sartans as monomedication [1,2], sartans in combination with thiazide diuretics [3,4], but also after monotherapy with thiazide diuretics [5-7]. While in the case of preparations containing sartans and thiazide diuretics and/or thiazide diuretics alone, this side effect could be explained by the possible photosensitizing effect of hydrochlorothiazide, in the case of monomedication with sartans one should also think about the role of additional factors—namely: possible contamination with nitrosamines, for example [1,2].

We present a patient who was taking several arterial hypertension medications: valsartan, valsartan/hydrochlorothiazide, and olmesartan, olmesartan/hydrochlorothiazide, and who developed a palmar verrucous carcinoma and a basal cell carcinoma in the neck during this treatment. Possible pathogenetic mechanisms for the staged development of keratinocytic tumors are discussed, with a focus on the current contamination with nitrosamines in high blood pressure medications.

**Case report.**

A 71-year-old male came to the dermatology department with primary complaints of a persistent pain in the left palm area, due to the presence of a non-healing wound, which occurred after planned radiotherapy in the same area (Figure 1).

**Figure 1.** Clinical picture showing a deep ulcerative wound at the site of a verrucous carcinoma removed years ago. Histopathological finding with evidence of postradiation dermatitis.

In 2015 the patient noticed in the left palm area the appearance of skin formations resembling warts, which gradually began to grow. He entered another hospital for treatment of the condition in 2018, where the formation was excised, histologically verified as verrucous squamous carcinoma (non in sano), after which he started a course of orthovolt percutaneous radiation, with a total of three courses of radiotherapy in 2018, 2019, and 2022.

In February 2023, he was hospitalized due to an infection of the wound, where incision, lavage and drainage were performed, as well as antibiotic therapy with intramuscular Amikacin 1000mg twice daily for a week, then switched to a reduced dose of 500mg twice daily for another 5 days. During the stay, a CT scan was performed, which ruled out the presence of metastases in connection with the initial tumor of the arm.

The patient came to the dermatology department due to a persistent ulceration measuring 3.0cm x 3.5cm, located at the excision site of the primary tumor and not healing for 8 months.

In addition, an arterial hypertension without congestive heart failure was diagnosed in 2015, for which he takes the following medications: from 2015 until 2018 – valsartan 160mg once in the morning; from 2018 until august 2022 – valsartan/hydrochlorothiazide 160mg/12.5mg once in the morning; from july 2022 until February 2023 - olmesartan medoxomil/amlodipine 20mg/5mg once in the evening and olmesartan medoxomil/hydrochlorothiazide 20mg/12.5mg; from February 2022 till today – olmesartan medoxomil/amlodipine 20mg/5mg once in the morning; and from 2015 – moxonidine 0.2mg once in the evening when needed.

The dermatological examination showed an ulcerative lesion with raised, whitish hyperkeratotic margins and deep penetration seen in the crease between the thumb and forefinger (Figure 1). Additionally, in the right cheek area, above the mandibula, a plaque with an irregular shape, dark pink color and a pearly edge, was observed, with suspicion for basal cell carcinoma. Enlarged lymph nodes were not palpable (Figure 2).

**Figure 2.** Preoperative clinical finding with clinical and dermatoscopic findings suggestive of pigmented basal cell carcinoma of the skin.

Routine laboratory tests were performed resulting without abnormalities. The ultrasound showed abdominal aorta with pronounced calcinosis and uneven outlines. Pronounced atheromatosis was established. The patient was recommended a change in the regime after the
surgical intervention: a medication that keeps the veins healthy, elastic and toned and clopidogrel 75mg.

Under local anesthesia, the patient underwent surgical excision of the supramandibular tumor-like formation on the right cheek area. Single interrupted sutures and adaptation of the wound edges were performed (Figure 3). Iodacept povidone dressings were made. The histopathological verification showed superficial multifocal basal cell carcinoma measuring 12/1mm, staged T1N0M0. Due to a suspicion of tumor recurrence of verrucous carcinoma in the palm area, two additional biopsies of the lesional skin were performed, resulting in a profuse parakeratosis with serous lacunae, horizontally alternating with compact orthohyperkeratosis, uniform acanthosis with moderate spongiosis, artificial intraepidermal clefting, densely chilinised papillary dermis with coagulation necrosis, obscuring the dermo-epidermal border. The histological constellation demonstrated sclerodermiform changes in the clinical context of chronic radiodermatitis.

Figure 3. Postoperative clinical finding after removal of basal cell carcinoma in the neck.

A change in the systemic therapy for the arterial hypertension was recommended with Verapamil hydrochloride 240mg once daily, spironolacton 50 mg once daily in the morning and doxazosin 4 mg once daily.

Discussion.

The problematic availability of nitrosamines in general, or their increased availability, stems from the fact that whether they are found in ranitidine, metformin, sartans, or thiazide diuretics, it is more than evident that they possess mutagenic activity and potentiate the generation of skin cancer [8,9].

Analogous data are found in their possible presence in ACE inhibitors such as enalapril and perindopril- single or multiple basal cell carcinomas, some of them metatypic [10,11].

It should be noted that these manifestations and associations- namely, between drug intake, potential/(currently actual and EMA-allowed) nitrosamine contamination, and keratinocytic cancer formation- could by no means be defined as sporadic.

There is evidence in the literature of the development of keratoacanthoma and verrucous carcinoma after the intake of a potentially/actually nitrosamine-contaminated combination preparation containing irbesartan and hydrochlorothiazide [12,13].

The occurrence of giant acral melanoma in combination with multiple verrucous carcinomas has also been described in the setting of olmesartan and valsartan therapy [14].

Monotherapy with valsartan , as well as the combination with a thiazide diuretic potentially/actually contaminated with nitrosamines, could lead to the manifestation of basal cell carcinomas [15,16].

Nitrosamine contamination continues to be a huge yet unsolved problem. More and more different classes of drugs appear to be affected by this contamination, and the exact mechanisms of its occurrence are unclear. This is what makes it difficult to eliminate this problem.

Pharmaceutical giant Pfizer is recalling certain lots of INDERAL LA (Propranolol hydrochloride) as early as 2022 due to nitrosamine contamination/ N-Nitroso propranolol/ and risk of cancer development [17]. Thus, betablockers also enter the group of drugs with permissive availability for nitrosamines. It is expected that this particular relationship will soon be thematized similarly to the others mentioned so far concerning ACE inhibitors, sartans and thiazide diuretics.

Thus, in practice, ACE inhibitors, thiazide diuretics as monotherapy or in combination with ACE inhibitors/ or with sartans, as well as sartan monotherapy, could be a risk factor with respect to the development of keratinocytic skin cancer [3-5,6,10,11-15]. The nitrosogenesis of skin cancer should become one of the most significant concepts in the near future, which will provide answers not only to the processes leading to the generation of keratinocytic tumors and melanoma, but also to a number of other cancers.

There is also no shortage of strong evidence from various European follow-up studies highlighting 1) the risk of developing/high mortality from tumours such as prostate cancer, pancreatic cancer, liver cancer, bladder tumours, lung cancer, stomach cancer, oesophageal cancer, multiple myeloma, leukaemia, following inhalation (in vivo) exposure to nitrosamines in occupational settings [18].

Other international observations (Sweden), again concerning intensive exposure (in vivo) of human subjects (Swedish rubber workers) to high doses of nitrosamines in a working atmosphere, emphasize the resulting direct risk of other severe symptoms: nosebleeds, eye and throat symptoms, hoarseness, cough, nausea, headache, and changed levels of eosinophils and total immunoglobulin G (IgG), compared with unexposed
Hydrochlorothiazide use is associated with the risk of cutaneous

VanWormer JJ, Abokede EB, Berg RL. Hydrochlorothiazide
use, sun exposure, and risk of keratinocyte cancer. BMC Public

There is also no shortage of single clinical observations
that similarly associate the development of colon cancer
and melanoma simultaneously after intake of potentially
nitrosamine-contaminated sartans and/or hydrochlorothiazide
(in vivo) [22,23].

Recent clinical trials' attempts to shift the blame for the
development of keratinocytic cancers and melanoma to its
known photosensitizing action alone [5] should not divert
clinicians' attention from the availability of nitrosamines in high
blood pressure medications.

These studies in no way provide an explanation for the
development of similar to completely analogous variants of
skin tumors that developed in the context of monotherapy with
sartans or metformin, for example [1,2,8,11], where the link
could be only one: the permissive availability of nitrosamines.

REFERENCES