Dear Editor,

An 80-year-old female presented to the dermatology department due to an atrophic lesion in the area of the nasal apex, dating for the past 5-6 years. Moreover, there was a slowly developing tumor-like growth in her left temporal region, initially noticed 1-2 years ago. Over the last month, the formation began to bleed upon light touch. Furthermore, there was another lesion in the sacral area with an irregular hyperpigmented edge, also dating back 1-2 years.

The patient denied having any allergies or family history of skin malignancies. Regarding comorbidities, she underwent cholecystectomy in 2016. She has been managing arterial hypertension with lisinopril dehydrate 10 mg once daily for the past 10 years. Additionally, she has been treating vertigo with a daily intake of betahistine dihydrochloride 16 mg for the same duration. She is also taking spironolactone 25 mg once daily at noon and diosmin 600 mg once daily at noon both for the past two months (prior to the consultation).

The patient presented with a request for physical evaluation of the lesions and further therapeutic approach to be established. The dermatological examination revealed a solitary lesion covered with brownish crusts in the left temporal region (Fig. 1a). An atrophic lesion, measuring 1 cm in diameter, characterized by superficial telangiectasias and a pearly edge, was observed in the area of the nasal apex (Fig. 2a). In the sacral area, a single lesion, measured 1 cm in diameter, with an irregular shape and an uneven hyperpigmented border, aligning with the surrounding skin, was observed (Fig. 3a). The lesions were suspected for basal cell carcinomas (BCCs). Additionally, multiple actinic keratoses were noted throughout the body. Lymph nodes were not palpable.

The patient denies suffering painful sunburns in the past. Routine blood tests were conducted, resulting without significant abnormalities. The patient was recommended treatment with several surgical excisions in two surgical sessions under local anesthesia for the problematic lesions.

During the surgical session, the lesions located on the left temporal (figure. 1b-d) and sacral regions (figure. 3a-c) were removed under local anesthesia using 1% lidocaine through elliptical excisions with an operative safety margin of 0.3 cm in all directions. Thorough hemostasis and closure of the defects were accomplished with single interrupted stitches (figure. 1d), (figure. 3c). The excised material was sent for histopathological verification, revealing basal cell carcinomas of the nodular and morpheaform types, both staged T1N0M0. Under local anesthesia, the lesion located on the nasal apex was removed through oval/ elliptical excision (figure. 2b), ensuring an operative safety margin of 0.3 cm in all directions. The remaining defect was addressed with an island flap and closed with single interrupted sutures (figure. 2c, d). Histopathological verification indicated an infiltrative basal cell carcinoma staged as T1N0M0. Clear resection lines.

UV radiation is a well-known predominant factor in photocarcinogenesis, contributing significantly to the development of skin cancer types like melanoma, squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) (1).

DNA damage is a result of UV radiation (1). Mutations can result in the inactivation of the tumor-suppressor genes, and when combined with the activated growth-promoting pathways, they contribute to the disruption of the cell-cycle progression (1). Specific genes are affected based on the skin cancer type (1).
Figure. 1a-d: A solitary lesion covered with brownish crusts in the left temporal region (a), removed with elliptical excision (b,c). The remaining defect was closed by single interrupted sutures (d).

P53 is often described as “the guardian of genome” (2). This transcription-suppressing factor plays a key role in the cell’s genomic integrity (2). Genetic alterations within the p53 tumor suppressor gene are strongly associated with cancer development, particularly common in skin cancer, where UV radiation serves as the leading cause of mutations resulting in oncogenic transformation (3).

P53 mutations can be detected in 50% of all human neoplasms and are present in 90% of the melanoma cases, making them the most prevalent genomic alterations in carcinomas (2).

Oncogenic mutations in RAS genes are present in over 30% of all human cancers (4). Ras point mutations are seen in melanoma and non-melanoma skin cancers, such as squamous cell carcinoma and keratoacanthoma (5).

Although photocarcinogenesis is widely recognized as a major factor in the initiation and progression of keratinocytic and
Multiple BCCs after Lisinopril Intake – Significant Connections to The Drug Related Photo-(Nitroso)-Carcinogenesis in The Context of Oncopharmacogenesis
melanocytic cancers by inducing a variety of mutations, such as in p53 (3), the fact that nitrosamines are also capable of inducing mutations in the p53 gene and the RAS oncogene should not be overlooked (6).

Extensive research over the years has thoroughly examined the impact of nitrosamine exposure on workers in the rubber industry (7). The data strongly indicates a substantial and concerning risk with the development of various types of cancer – cancers affecting the esophagus, oral cavity, pharynx, lungs, stomach, bladder, prostate, liver, pancreas; as well as multiple myeloma, leukemia and other malignancies (7),(8),(9). A direct correlation between the intake or inhalation of nitrosamines and the onset of diverse cancer forms was established a substantial time ago (7).

Nitrosamines are potent carcinogens (10). Relatively recently, nitrosamine contamination was detected in several medications prescribed for conditions such arterial hypertension and type 2 diabetes, leading to numerous Food and Drug Administration (FDA) recalls in the United States (10). The contamination included different nitrosamines such as N-nitrosodimethylamine (NDMA), N-nitrosodimethyleamine (NDEA), N-nitroso-N-methyl-4-aminobutyric acid (NMBA) and others (10). The results from Li et al. (10) revealed for NDMA, the estimated cancer risk ranged from 40 to 126 additional cancer cases per 100,000 exposed individuals and for NDEA, the estimated cancer risks ranged from 12 to 48 additional cancer cases per 100,000 exposed individuals. Intriguingly, the case study calculated the NDMA and NDEA risks separately, taking into account the assumption of exposure to only one nitrosamine in a given drug product (10). Remarkably, there has been minimal global research to date discussing the influence of nitrosamines in polymedication concerning skin cancer, with only a few publications delving into this matter (11),(12). It would be important to note that carcinogenic action should not always overlap with mutagenic action, even sometimes this is quite possible. And Nitrosogenesis could be associated with "both of them".

The term Nitrosogenesis has been introduced recently in the context of nitrosamines/nitrosamine drug substance-related impurities (NDSRIs) in polymedication/polycontamination in polymorbid patients (11). A more modern perspective now suggests that the risk of developing heterogenous types of cancers, including both keratinocytic and melanocytic cancers, is largely influenced by exposure to multiple carcinogens in the context of polycarcinogenesis in polymedication (11). Unfortunately, the association between nitrosamine intake and cancer development...
was categorized by some colleagues as either possible, probable or presently not relevant (13), until now.

However, certain collectives shed light on the issue and the once-considered “possible” association no longer appears so “irrelevant” (14-17). These findings are based on the clinicopathological correlations following the intake of potentially nitrosamine-contaminated products and the subsequent development of skin cancer. Instead, their observations are rooted in the dose-dependent time intervals from drug intake to the onset of skin cancer development (14-17).

This is important and significant as previous international studies have also found an association between the intake of ACE inhibitors and an increased incidence of keratinocytic cancer (18).

Nardone B et al. (18) highlighted a notable risk associated with the development of BCC following the use of ACE inhibitors: unadjusted OR (95% CI) 2.09 (1.87-2.34) and adjusted OR (95% CI) 2.23 (1.78-2.81) for age, gender, race and CCI.

Similarly, in the study done by Mehlan et al. (19), the emergence of keratinocyte cancers is linked to the use of ACE inhibitors and hydrochlorothiazide.

However, both articles do not specifically address the potential contamination with nitrosamines as a possible cofactor but rather emphasize the particular attention to the probable photosensitizing effect of the medications (18,19).

Contrary to this preposition, two observations or counterarguments challenge it: 1) some patients described in the literature were not exposed to ultraviolet radiation in their entire lives and 2) despite the widespread emphasis on sunburn prevention in recent years through media, conferences, and campaigns, the incidence of cancer is not decreasing. In fact, contrary to expectations, it is on the rise (20).

The global incidence rate for keratinocyte cancer varies significantly, with Australia having the highest rate at 2,448 cases per 100,000 people developing BCC (21). In Europe, the rates are 129.3 in men and 90.8 in women per 100,000 people, while in the US, it is 450 cases per 100,000 people (21).

The cause of cancer may extend beyond painful sunburn, possibly involving other pathogenetic or more significant factors. It is here that the inclusion of nitrosamines in the medications crystallizes their largely pathogenetic role (22), as their intake over a relatively short period of time can lead to the onset of keratinocytic cancer, but not only.

We present an 80-year-old female with multiple BCCs following Lisinopril intake, effectively treated with undermining surgery. The residual defect of the lesion located on the nasal apex was successfully closed using an innovative yet efficient approach: a modified island flap. The discussion was centered around a novel perspective on cancer development – namely, the concept of “Drug related Nitrosogenesis” and the link to the Carcinogenesis/Mutagenesis. The dramatic increase in exposure to nitrosamines...
Multiple BCCs after Lisinopril Intake – Significant Connections to The Drug Related Photo-(Nitroso)-Carcinogenesis in The Context of Oncopharmacogenesis

in medications is now widely recognized as a growing global concern driving the new cancer pandemic, including that of keratinocyte cancer. The refusal of manufacturers and regulators to formally acknowledge the presence of these established carcinogens in drugs raises concerns and fosters suspicion among clinicians and patients.

Of considerable interest is the recently formalized photocarcinogenicity of N-nitrosomorpholine after irradiation with UVA (23). To what extent the photocarcinogenic effect of this nitrosamine is valid for other members of the nitrosamine family remains unclear, but is quite possible. The fact that certain nitrosamines (tobacco specific nitrosamines/TSNAs) are also potent photocarcinogens, analogous to N-nitrosomorpholine (23). Whether they are the leading ones remains to be elucidated.

Photocarcinogenesis, concerning the initiation of keratinocytic tumors and basal cell carcinomas in particular, also affects p53 and RAS oncogenes (25, 26).

The overlap of some of the mutational patterns of nitrosamine-induced mutations (TSNAs) (24) with those of basal cell carcinomas arising during photocarcinogenesis (25,26) suggests that, in all likelihood, the nitrosamines in drug preparations are also potent photocarcinogens, analogous to N-nitrosomorpholine (23). Whether they are the leading ones remains to be elucidated.

Drug-mediated Photo-(Nitroso)-carcinogenesis is a concept that should be studied in detail. This concept appears in all drug-mediated Photo-(Nitroso)-carcinogenesis is a concept that should be studied in detail. This concept appears in all

References

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