

Multiple BCCs after Lisinopril Intake – Significant Connections to The Drug Related Photo-(Nitroso)-Carcinogenesis in The Context of Oncopharmacogenesis

Kordeva S¹, Parambi S², Ivanov L³, Khanom S¹, Tchernev G^{1*3}

¹Onkoderma- Clinic for Dermatology, Venereology and Dermatologic Surgery, 26 General Skobelev Blvd. 1606 Sofia Bulgaria

²Independent researcher United Kingdom/ UK

³Department of Dermatology and Venereology, Medical Institute of Ministry of Interior, 79 General Skobelev Blvd, 1606, Sofia Bulgaria

Received: February 15, 2024; Accepted: February 25, 2024; Published: March 09, 2024

***Corresponding author:** Onkoderma- Clinic for Dermatology, Venereology and Dermatologic Surgery, 26 General Skobelev Blvd.1606 Sofia, Bulgaria. Department of Dermatology and Venereology, Medical Institute of Ministry of Interior, 79 General Skobelev Blvd.1606, Sofia. Bulgaria. Phone: 00359885588424, E-mail: georgi_tchernev@yahoo.de

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







Figure. 2a-d: 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 (a). The lesion was removed through elliptical/ oval excision (b), and the remaining defect was addressed with an island flap (c) and closed with single interrupted sutures (d). (e) Postoperative image after 4 weeks.

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 as 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-nitrosodiethylamine (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 heterogeneous types of cancers, including both keratinocytic and melanocytic cancers, is largely influenced by exposure to multiple carcinogens in the context of polycontamination in polymedication (11). Unfortunately, the association between nitrosamine intake and cancer development

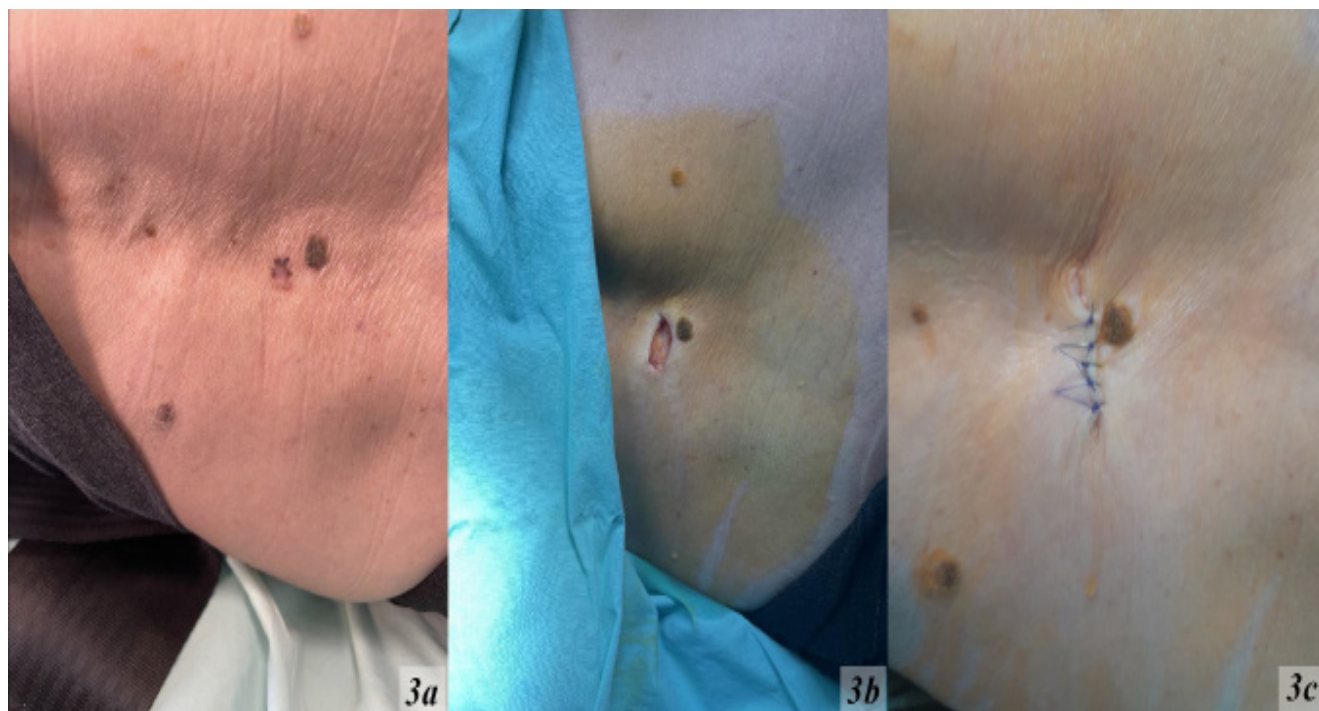


Figure. 3a-c: A single lesion, measured 1 cm in diameter, located in the sacral area, with an irregular shape and an uneven hyperpigmented border, aligning with the surrounding skin (a). The lesion was removed with an elliptical excision (b) and the remaining defect was closed by single interrupted sutures (c).

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

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 proven human carcinogens that induce mutations in p53 and RAS oncogenes has been known for decades (24).

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 likelihood to be inextricably linked to the onco-pharmacogenesis of keratinocytic cancer (27,28).

References

1. Martens MC, Seebode C, Lehmann J, Emmert S. Photocarcinogenesis and Skin Cancer Prevention Strategies: An Update. *Anticancer Res.* 2018 Feb;38(2):1153-1158. doi: 10.21873/anticancer.12334
2. Ananiev J Tchernev G, Patterson JW, Gulubova, M, Ganchev G. P53 – “THE GUARDIAN OF GENOME”. 2011 *Acta Med Bulg.* 2011; 38 (2): 72-82.
3. Benjamin CL, Ananthaswamy HN. p53 and the pathogenesis of skin cancer. *Toxicol Appl Pharmacol.* 2007 Nov 1; 224(3):241-248. doi: 10.1016/j.taap.2006.12.006
4. Hobbs GA, Der CJ, Rossman KL. RAS isoforms and mutations in cancer at a glance. *J Cell Sci.* 2016 Apr 1; 129(7):1287-1292. doi: 10.1242/jcs.182873
5. Wilke WW, Robinson RA, Kennard CD. H-ras-1 gene mutations in basal cell carcinoma: automated direct sequencing of clinical specimens. *Mod Pathol.* 1993 Jan;6(1):15-19.
6. Chang KW, Sarraj S, Lin SC, Tsai PI, Solt D. P53 expression, p53 and H-ras mutation and telomerase activation during nitrosamine-mediated hamster pouch carcinogenesis. *Carcinogenesis.* 2000 Jul; 21(7):1441-1451.
7. Hidajat M, McElvenny DM, Ritchie P, Andrew D, William M et al. Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow-up. *Occup Environ Med.* 2019 Apr;76(4):250-258. doi: 10.1136/oemed-2018-105181
8. Straif K, Weiland SK, Bungers M, D. Holthenrich, D. Taeger, S. Yi et al. Exposure to high concentrations of nitrosamines and cancer mortality among a cohort of rubberworkers. *Occup Environ Med.* 2000 Mar; 57(3):180-187. doi: 10.1136/oem.57.3.180
9. Nutt A. Rubber work and cancer--past, present and perspectives. *Scand J Work Environ Health.* 1983;9 Suppl 2:49-57
10. Li K, Ricker K, Tsai FC, Hsieh CJ, Osborne G, et al. Estimated Cancer Risks Associated with Nitrosamine Contamination in Commonly Used Medications. *Int J Environ Res Public Health.* 2021 Sep 8;18(18):9465. doi: 10.3390/ijerph18189465
11. Tchernev G. NITROSAMINES IN COMMONLY PRESCRIBED ANTIHYPERTENSIVES AND THE (UN) CONTROLLED DRUG-INDUCED SKIN CANCER: SIMULTANEOUS DEVELOPMENT OF CUTANEOUS MELANOMA AND MULTIPLE BCC AFTER CONCOMITANT ADMINISTRATION OF BISOPROLOL AND FUROSEMIDE. *Georgian Med News.* 2023 Sep ;(342):149-151.
12. Tchernev G. NITROSOGENESIS OF SKIN CANCER: THE NITROSAMINE CONTAMINATION IN THE CALCIUM CHANNEL BLOCKERS (AMLODIPINE), BETA BLOCKERS (BISOPROLOL), SARTANS (VALSARTAN/LOSARTAN), ACE INHIBITORS (PERINDOPRIL/ENALAPRIL), TRICYCLIC ANTIDEPRESSANTS (MELITRACEN), SSRIS (PAROXETINE), SNRIS (VENLAFAXINE) AND METFORMIN: THE MOST PROBABLE EXPLANATION FOR THE RISING SKIN CANCER INCIDENCE. *Georgian Med News.* 2023 Jun;(339):24-32.
13. Kordeva S, Cardoso J, Tchernev G. CONGRESS REPORT OF THE 5TH NATIONAL CONGRESS OF THE BULGARIAN SOCIETY FOR DERMATOLOGIC SURGERY, SOFIA, 11TH MARCH 2023 WITH MAIN TOPICS: NITROSAMINES AS MOST POWERFUL TRIGGER FOR SKIN CANCER DEVELOPMENT AND PROGRESSION/PERSONALISED ONE STEP MELANOMA SURGERY AS POSSIBLE SKIN CANCER TREATMENT OPTION. *Georgian Med News.* 2023 Apr;(337):89-95.
14. Tchernev G, Kordeva S. NITROSOGENESIS OF SKIN (HUMAN) CANCER- THE HIDDEN TRUTH OF A NEVERENDING STORY: NITROSAMINE CONTAMINATION IN OLMESARTAN, VALSARTAN AND HCT AS MAIN RISK FACTOR FOR THE DEVELOPMENT OF KERATINOCYTE CANCER. *Georgian Med News.* 2023 Apr;(337):63-67.
15. Tchernev G, Kordeva S. MULTIPLE BCCS AND DYSPLASTIC NEVI AFTER ACE INHIBITORS (ENALAPRIL/PERINDOPRIL): THE ROLE OF NITROSAMINE CONTAMINATION/AVAILABILITY AS SUBSTANTIAL SKIN CANCER TRIGGERING FACTOR. *Georgian Med News.* 2023 Feb;(335):90-94.
16. Tchernev G, Kordeva S, Lozev I. METATYPICAL BCCS OF THE NOSE TREATED SUCCESSFULLY VIA BILOBED TRANSPOSITION FLAP: NITROSAMINES IN ACES (ENALAPRIL), ARBS (LOSARTAN) AS POSSIBLE SKIN CANCER KEY TRIGGERING FACTOR. *Georgian Med News.* 2023 Feb;(335):22-25.
17. Tchernev G, Lozev I, Pidakev I, Kordeva S. KARAPANDZIC FLAP FOR SQUAMOUS CELL CARCINOMA OF THE LOWER LIPP: POTENTIAL ROLE OF NITROSAMINES IN EPROSARTAN AS CANCER TRIGGERING FACTORS. *Georgian Med News.* 2023 Jan;(334):83-85.
18. Nardone B, Majewski S, Kim AS, Kiguradze T, Martinez-Escala EM,

- et.al Melanoma and Non-Melanoma Skin Cancer Associated with Angiotensin-Converting-Enzyme Inhibitors, Angiotensin-Receptor Blockers and Thiazides: A Matched Cohort Study. *Drug Saf.* 2017 Mar;40(3):249-255. doi: 10.1007/s40264-016-0487-9
19. Mehlan J, Ueberschaar J, Hagenström K, Garbe C, Spitzer MS, et.al. The use of HCT and/or ACE inhibitors significantly increases the risk of non-melanotic skin cancer in the periocular region. *Graefes Arch Clin Exp Ophthalmol.* 2022 Aug;260(8):2745-2751. doi: 10.1007/s00417-022-05576-y
20. Halpern AC, Kopp LJ. Awareness, knowledge and attitudes to non-melanoma skin cancer and actinic keratosis among the general public. *Int J Dermatol.* 2005 Feb;44(2):107-11. doi: 10.1111/j.1365-4632.2005.02090.x
21. Apalla Z, Lallas A, Sotiriou E, Lazaridou E, Ioannides D. Epidemiological trends in skin cancer. *Dermatol Pract Concept.* 2017 Apr 30;7(2):1-6. doi: 10.5826/dpc.0702a01
22. Tchernev G, Kordeva S, Patterson JW. Nitrosamines and skin cancer: rather reality than a myth? *J Med Review (Bulgarian).* 2023;59:5-7.
23. Mochizuki H, Nagazawa Y, Arimoto-Kobayashi S. Genotoxicity and the stability of N-nitrosomorpholine activity following UVA irradiation. *Mutat Res Genet Toxicol Environ Mutagen.* 2024 Jan; 893: 503721. doi: 10.1016/j.mrgentox.2023.503721
24. Stanfill SB, Hecht SS, Joerger AC, González PJ, Maia LB, et.al From cultivation to cancer: formation of N-nitrosamines and other carcinogens in smokeless tobacco and their mutagenic implications. *Crit Rev Toxicol.* 2023 Nov;53(10):658-701. doi: 10.1080/10408444.2023.2264327
25. Martens MC, Seebode C, Lehmann J, Emmert S. Photocarcinogenesis and Skin Cancer Prevention Strategies: An Update. *Anticancer Res.* 2018 Feb;38(2):1153-1158. doi: 10.21873/anticancer.12334
26. de Gruijl FR. Photocarcinogenesis: UVA vs. UVB radiation. *Skin Pharmacol Appl Skin Physiol.* 2002 Sep-Oct;15(5):316-20. doi: 10.1159/000064535
27. Tchernev G, Todorov I, Ivanov L, Kordeva S. Basal cell carcinoma development after combined administration with Lisinopril and Tamsulosin: significant links to Photocarcinogenesis and Nitrosogenesis in the context of Pharmacology-Oncogenesis. *J Medicinski pregled (Bulgarian)* 2024; 60 (4): 48-54.
28. Tchernev G, Naydekova N, Ivanov L, Kordeva S, Simon AC. ENIGMATIC LESSONS FROM DERMATOLOGISTS: PHARMACO-ONCOGENESIS AND NITROSOGENESIS OF SKIN CANCER: FACTS AND CONTROVERSIES. *J Medicinski pregled (Bulgarian)* 2024; 60 (3): 67-72.