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CASE REPORT

CHEEK ADVANCEMENT FLAP FOR BCC OF THE NOSE: THE NITROSAMINE CONTAMINATION DURING THE COMBINED DRUG INTAKE AS IMPORTANT SKIN CANCER TRIGGERING FACTOR

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Abstract. *The emerging insights and (hypo)theses regarding the pathogenesis of skin cancer are particularly intriguing, as they introduce a novel and unconventional etiopathogenetic factor: the presence of contaminants, specifically nitrosamines, in medications for high blood pressure, diabetes mellitus and many others. The combined use of potentially or actually contaminated preparations creates conditions for the simultaneous intake of multiple carcinogens, some of which possess both genotoxic and phototoxic properties. The authorisation regimes for the availability, but also for the daily, prolonged, "officially undisclosed" intake of nitrosamines heterogeneous in type and carcinogenicity in medicines are based on: the determination of their carcinogenic potency based on a specific test in: 1) bacteria/Ames Test and/or the search for an analogue of carcinogenicity in 2) rodents/CPCA Test. However, the interpretations of the results of these tests should in no way be regarded as reciprocal in humans. The processes of "human carcinogenesis" are dynamic and multifactorial and could not be characterized by interpretation or equivalence of results from "static tests" conducted in bacteria and/or rodents. Moreover, these tests do not analyse the concurrent intake or simultaneous action of several carcinogens (referring here specifically to the polycontamination of polymedication) on a given, be it unicellular, multicellular, rodents or even human organism. In practice, these tests paraphrase or betonate carcinogenic availability in drugs as being alternativeless, but remaining at the same time classified for the medical personnel and the final users. We describe a 74-year-old male with arterial hypertension and diabetes, undergoing systemic therapy with losartan/hydrochlorothiazide, nifedipine, moxonidine, metoprolol, glimepiride and metformin, who subsequently developed 18 cutaneous cancers – 2 basal and 16 squamous carcinomas – over a 5-year period. The article also discusses the treatment of the last cutaneous tumor located on the left nasal sidewall, successfully managed using a cheek advancement flap. It further explores the role of drug-mediated Nitrosogenesis and Photo-Nitroso-Carcinogenesis. The broad base of the pyramid of drug-mediated carcinogenesis/nitrosogenesis underlying skin cancer pathogenesis could be conditioned by: 1) the presence of phototoxic but at the same time 2) genotoxic substances, also known for decades as nitrosamines. Regardless of the class of drugs in which these mutagens and (to some extent) photocarcinogens are found (antidiabetic, antihypertensive or antiarrhythmic drugs, but also a number of others), their pro-carcinogenic action in all likelihood appears to be pathogenetically associated/related to the generation of the same tumors: keratinocytic. Whether the nitrosamines are the only substances in the drugs determining the phototoxicity, genotoxicity and subsequent photocarcinogenicity remains hanging in the scientific space with full force, but also with a decreasing amount of doubt.*

Key words: *skin cancer, Photocarcinogenesis, metabolic reprogramming, Drug related Nitrosogenesis, Losartan/Hydrochlorothiazide, Nitroso-nifedipine, nitroso-moxonidine, nitroso-metoprolol, Nitroso-metformin, cheek advancement flap, dermatologic surgery*

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INTRODUCTION

Cumulative UV radiation, particularly UVB wavelengths, along with genetic predisposition [1], fair complexion (especially red hair), certain skin types (Fitzpatrick types 1 and 2), and a history of painful sunburns in childhood, are well-established risk factors contributing to the development of keratinocyte tumors [2]. However, these factors do not sufficiently explain the substantial rise in skin cancer incidence observed in recent years [3, 4]. There are likely other factors influencing photosensitivity and photocarcinogenicity – concepts that remain unclear but are likely linked in some way to the frequency of both melanocytic and keratinocytic cancers.

Recent hypotheses, although still speculative according to some colleagues and scientists, suggest a potential association between the development of skin cancer and the intake of nitrosamine-contaminated polymedication, within the context of polymorbidity [5, 6]. The combined intake of multiple potentially contaminated medications, as indicated by existing data, poses a risk for the development for both keratinocyte cancers [5, 6] and melanoma [7]. Although the study focused on exposure to a single product contaminated with one nitrosamine – NDMA-contaminated valsartan – nitroso contamination remains a recognized potential risk factor [7]. Furthermore, the study lacked data on the use of potentially contaminated co-medication, as per the FDA lists from 2019 and 2023 [8].

Nitrosamines have been recognized as possible strong human carcinogenes for over 50 years [9], with their phototoxicity described as a nonspecific effect related to photodecomposition of the nitroso group [10]. Unfortunately, even today, this data remains largely ignored, although representatives of this carcinogen group are present in medications for high blood pressure, but not only [11].

It is not surprising that the simultaneous intake of four medications, each containing one or two carcinogens (nitrosamines with potential genotoxic) phototoxic effects, contributes to the development of skin cancers, including recurrent keratinocyte cancers as observed in our patient, as well as both single and multiple melanomas [12, 13].

Findings established since 1972 [10] are still being overlooked, even though these or similar contaminants are present in over 300 widely distributed drugs, as listed by the FDA, and are used by approximately 4 billion patients globally [8]. These drugs contain an indeterminate number of nitrosamines/NDSRIS, many of which remain largely unidentified, but should be classified as carcinogens, mutagens, genotoxic substances, and/or photocarcinogens.

We present a 74–year–old male with 18 cutaneous cancers that developed in the context of potentially/really contaminated polymedication, including antidiabetic and antihypertensive medications. The role of drug-induced nitrosogenesis, photocarcinogenesis and oncopharmacogenesis within the short-term development of multiple keratinocyte tumors is discussed.

CASE REPORT

A 74-year old male presented to the dermatology department with primary complaints of an ulcerative neoplasm on the nasal dorsum, with history of three previous surgeries in the same region for recurrent squamous cell carcinomas (SCCs).

He reported a total of 17 surgical interventions performed on his facial and auricle areas for various cutaneous tumors between 2020 and 2024, as follows:

- in June 2020 – right cheek – SCC, left cheek – SCC, and nose – SCC, all excised with clear resection margins; in October 2021 – left auricle – SCC, left auricle (second location) – SCC, cartilage of the left auricle – SCC, right facial area – SCC, and left facial area – basal cell carcinoma (BCC), all with clean resection margins;

- in December 2021 – right temporal region – SCC, lower left eyelid – SCC, right facial area – SCC, and right auricle – SCC, all removed with clear resection margins;
- in August 2022 – tumor formation in the left temporal region, tumor formation in the left periauricular region, and tumor formation in the right preauricular area resulting in moderately differentiated SCCs; and
- in February 2024 – poorly differentiated G1 squamous cell carcinoma excised from the right lower eyelid T1N0M0R1 and in the temporal region a well differentiated G1 SCC was excised with clean resection margins, staged as T1N0M0R0.

The patient reported having arterial hypertension since 1995 and diabetes since 1992. He underwent a prostatectomy in 2023. Additionally, he had a history of working outdoors and previous sunburns.

For the arterial hypertension, the patient was on systemic medication with losartan potassium/hydrochlorothiazide 50/12.5 mg once daily in the morning for over 10 years, nifedipine 20 mg twice daily – once in the morning and once in the evening for over 10 years, moxonidine 0.2 mg twice daily – once in the morning and once in the evening for over 5 years, and metoprolol tartrate 50 mg half a tablet once daily for the past 3 years; For his diabetes he has been taking glimepiride 3 mg once daily for 15 years, along with metformin hydrochloride 850mg three times a day for 15 years. Additionally, he has been taking pentoxifylline 400 mg once daily and thioctic acid 600 mg once daily, both administered for 20 years.

The patient requested physical evaluation and further therapeutic approach to be established.

The dermatological examination revealed an ulcerated neoplasm on the dorsum nasi, persisting for the past 6-7 months (Fig. 1). Enlarged lymph nodes were not palpable. The routine laboratory tests showed no abnormalities. According to the clinical and anamnestic data, a basal cell carcinoma was suspected. The patient was recommended surgery under local anesthesia for the suspected lesion.

Under local anesthesia with 2% lidocaine, an oval and sickle-shaped excision of the nasal tumor was performed (Fig. 2).

An advancement flap was designed for the reconstruction of the remaining oval defect on the left nasal sidewall, with the cheek area serving as the donor site (Figures 3-4).

Fig. 1. Preoperative view: an ulcerated lesion located on the nasal dorsum

Fig. 2. Intraoperative view: Primary skin defect following tumor excision on the nasal dorsum

Fig. 3. Intraoperative view: Secondary skin defect following the design of the cheek advancement flap in order to close the primary skin defect

Fig. 4. Intraoperative view: Secondary skin defect following the design of the cheek advancement flap in order to close the primary skin defect

The secondary defect was further closed by single interrupted sutures (Figures 5-6). A sterile wound dressing was applied. Metamizole sodium ampoules were added to the therapy as needed. The excised materials were sent for histopathological evaluation, which revealed an infiltrative (high-risk) basal cell carcinoma (T1N0M0).

DISCUSSION

The international community has revised its perspective on drug-induced cancer, now linking the use of antihypertensive medications to the development of skin cancer [14-16].

Certain antihypertensive medications are well-known for their photosensitizing properties, with hydrochlorothiazide documented as a cause of phototoxic and photoallergic skin eruptions [14]. In the context of polymorbidity and the concurrent use of multiple photosensitizing antihypertensive medications, it is logically expected that the risk of developing skin cancer would increase [14]. The study conducted by Cohen et al [14] reported increased risks for various skin cancers associated with different classes of antihypertensive medications.

Specifically, the relative risk (RR) for basal cell carcinoma was elevated with calcium channel blockers (relative risk [RR] = 1.17, 95% confidence interval [CI] = 1.11-1.22), diuretics (RR = 1.06, 95% CI = 1.03-1.10), and thiazides (RR = 1.10, 95% CI = 1.04-1.16) [14].

For squamous cell carcinoma the risk was higher with calcium channel blockers (RR = 1.08, 95% CI = 1.01-1.14), diuretics (RR = 1.29, 95% CI = 1.17-1.43), and thiazides (RR = 1.36, 95% CI = 1.15-1.61) (14). For melanoma, increased risks were noted with angiotensin-converting enzyme inhibitors (RR = 1.09, 95% CI = 1.03-1.14), calcium channel blockers (RR = 1.08, 95% CI = 1.03-1.12), and thiazides (RR = 1.09, 95% CI = 1.02-1.17) [14]. The article also provided evidence of a dose-response relationship between thiazide use and basal cell carcinoma, as well as between angiotensin-converting enzyme inhibitors, diuretics, and thiazides with squamous cell carcinoma [14].

Additionally, a dose-response relationship was observed for angiotensin-converting enzyme inhibitors, diuretics, and thiazides with melanoma [14].

Fig. 5. Intraoperative view: The remaining skin defect was closed with single interrupted sutures. Frontal view

Fig. 6. Intraoperative view: The remaining skin defect was closed with single interrupted sutures. Lateral view

Our patient is undergoing systemic therapy that, in addition to the other medications detailed in the case report (which will be discussed later in the article), includes a combination preparation containing hydrochlorothiazide (diuretic) and a nifedipine (calcium-channel blocker). Both preparations – N-nitroso-hydrochlorothiazide, with a predicted carcinogenic potency categorization of 4 and recommended AI limit of 1500 ng/day, and N-nitroso-nifedipine, with a predicted carcinogenic potency categorization of 5 and recommended AI Limit of 1500 ng/day – are listed on the FDA's list "Recommended Acceptable Intake Limits for certain hypothetical NDSRIs" [8].

Prospective data from Hou et al [15] included 8,777 NMSC cases among postmenopausal women aged 50-79 years at baseline (n = 64,918). The study estimated that the use of antihypertensives (HR [95% CI]: 1.12 [1.07-1.18]), ACE inhibitors (1.09 [1.01-1.18]), calcium channel blockers (1.13 [1.05-1.22]), diuretics (1.20 [1.12-1.27]), loop diuretics (1.17 [1.07-1.28]), and thiazides (1.17 [1.03-1.33]) were each associated with a higher risk of NMSC [15]. The risk of non-melanoma skin cancer increased linearly with the use of multiple antihypertensives (p-trend = 0.02) and with longer duration of use (p-trend < 0.01) [15].

So far, we have established that hydrochlorothiazide is a risk factor for both keratinocytic (squamous and basal cell carcinomas) and melanocytic cancers [14, 15].

Another emerging cutaneous tumor entities, also induced by ultraviolet exposure, are the atypical fibroxanthoma (AFX) and pleomorphic sarcoma (PDS) [16]. A study by Kuntz et al (16) demonstrated that the use of hydrochlorothiazide was associated with an increased risk of atypical fibroxanthoma and pleomorphic dermal sarcoma. According to the same study, diabetes mellitus or its comorbidities could be linked to an elevated risk of developing AFX/PDS [16]. Specifically, these comorbidities often involve the use of additional medications like metformin and glimepiride. Although glimepiride is not included on the FDA's list of potentially contaminated drugs [8], the possibility of N-Nitroso Glimepiride contamination [17] cannot be entirely ruled out.

Metformin is already associated with the development of both keratinocyte and melanocytic cancers, primarily due to contamination with nitrosamines [18, 19]. According to the above, the carcinogenic potential of the drug is attributed to contaminants rather than the pure substance itself. The imbalance between the drug's therapeutic benefits and its risks may be explained by the presence of nitrosamines as contaminants. When metformin is used alongside other medications, such as those potentially contaminated with nitrosamines [8], there is a risk of simultaneous and continuous exposure to one or multiple carcinogens, which could further lead to the development of multiple keratinocyte tumors, as observed in our patient.

In a retrospective study by Sharma et al [20], a total of 4,464,148 spontaneous cases of adverse reactions were reported, of which 232,506 (5.20%) were neoplasm-related/ (angiotensin receptor blockers related also). Angiotensin Receptor Blockers (ARBs) were involved in 68,522 spontaneous cases (azilsartan, n = 492; candesartan, n = 12,322; irbesartan, n = 6413; olmesartan, n = 12,417; losartan, n = 12,032; valsartan, n = 18,950 and telmisartan, n = 5886) among which 3396 (5%) cases were reported of as "suspected" of neoplasm (azilsartan, n = 14; candesartan, n = 233; irbesartan, n = 195; olmesartan, n = 323; losartan, n = 616; valsartan, n = 1826 and telmisartan, n = 189) (20). Valsartan exhibited the highest reported odds ratio (ROR) for neoplasm among the ARBs (ROR 1.949, 95% CI 1.857-2.046) [18]. According to the study, this association remained significant when ARBs were compared to other antihypertensive drug classes, including ACE inhibitors, beta-blockers, calcium channel blockers, and diuretics [20].

A combined preparation containing losartan (ARBs) was used in our patient's therapeutic regimen. In addition, the FDA recalled several ARBs – valsartan, losartan and irbesartan – from the market due to the presence of nitrosamine impurities, including N-Nitrosodimethylamine (NDMA), and N-Nitrosodiethylamine (NDEA), which are probable human carcinogens, and N-Nitroso-N-methyl-4-aminobutyric acid (NMBA), which is classified as a potential human carcinogen [21].

Although moxonidine is not on the FDA's list of potentially contaminated drugs, data suggest that its use may be linked to an increased risk of developing high-risk basal cell carcinoma after additional/parallel intake with other (potentially contaminated) medications [11]. N-nitroso-metoprolol (a beta blocker) is currently listed by the FDA with a potency category of 4 and recommended AI limit of 1500 ng/day (8). International data is not lacking regarding the link between systemic intake of beta blockers and the subsequent development of skin cancer [5].

Based on the data discussed above, which associates the use of certain antihypertensive medications with the development of both keratinocytic and melanocytic cancers, as highlighted by the latest meta-analysis [14], but also by numerous case reports [22-25], it is suggested that a common factor – possibly nitrosamines, like N-nitrosomorpholine [26] – may underlie these events, contributing to both photosensitivity and carcinogenicity.

The genotoxicity and stability of N-nitrosomorpholine (NMOR) activity following UVA irradiation in the absence of metabolic activation was investigated in a study by Mochizuki et al [26]. In the performed Ames test, following UVA irradiation, the irradiated NMOR was found to be directly mutagenic, independent of UVA or metabolic activation [26]. Even after 10 days of storage at 37 °C, 4 °C, or -20 °C, the activity of NMOR was considered stable, remaining at 79%. Micronuclei formation was detected in vivo in the peripheral blood reticulocytes of mice injected with irradiated NMOR under inhibition of cytochrome P450-mediated metabolism of NMOR. The genotoxic effects of irradiated NMOR could be harmful if airborne pollutants containing photoactivated NMOR come into contact with the human body [26]. N-nitrosomorpholine was detected in a molsidomine tablet sample, which contained 144% of the recommended toxicological intake limit for NMOR [27]. The same article reported both an existing and recently identified contamination of losartan with two nitroso compounds – N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA), simultaneously [27]. However, one of them (N-nitrosodimethylamine) directly activates RAS oncogenes prior to metabolic processing and continues to exhibit mutagenic properties afterwards [28]. In practice, and according to official data, this suggests that the intake of losartan and metformin, could be associated with exposure to at least three different carcinogens [27], which, during both the pre- and post-metabolic phases, could enhance their overall carcinogenic potency. Photocarcinogenesis and nitrosamine exposure are increasingly being associated, with the potential for broader confirmation through future large-scale studies.

The patient we present, although as a case report, confirms the thesis stated by larger prospective studies that long-term (10-20 years) intake of potentially polycontaminated medications with nitroso compounds leads to recurrent forms of keratinocyte skin cancer. The patient had a history of 18 surgical interventions for various cutaneous tumors, including 2 basal and 16 squamous cell carcinomas, over a 5-year period.

The value of these cases and analyses lies in their potential to draw conclusions for much larger datasets based on findings from a small number of patients.

Case reports or series with retrospective/prospective nature seems to be sometimes crucial and carry more significance than purely prospective studies. This is because pharmaceutical conglomerates are unlikely to provide potentially contaminated products for testing in real patients, and such studies are often not regulated/monitored. Moreover, these case reports or series must hold more value than purely retrospective studies, which generally have greater importance than prospective ones due to the uncertainty of what will be tested 15 years into the future. However, in retrospective studies, patient groups or databases can be selectively chosen, or patients can be selectively involved.

The disadvantage of purely retrospective studies lies in the absence of real-time, verified data, which can undermine their credibility. Due to these limitations, cases with retrospective/prospective nature are of significant importance for the comprehensive evaluation of the multifactorial/dynamic processes of carcinogenesis, particularly in the context of the metabolic reprogramming of future tumor cells [29].

Considering the patient’s extensive history of 18 surgical interventions for cutaneous tumors (two basal and sixteen squamous cell carcinomas) and the prolonged intake of six potentially nitrosamine-contaminated medications (losartan/HCT, nifedipine, moxonidine, metoprolol, glimepiride and metformin), the association between nitrosamine-contamination and subsequent skin cancer development, becomes increasingly evident. At the time of concomitant drug intake, the patient developed permanent skin tumors, described again by us in various publications. Failure to discontinue this permanent, regular, potentially nitrosamine-contaminated, unofficially disclosed drug intake leads to the development of recurrent epithelial skin tumours. This intake appears to be in addition to permanent regulatory dilemma, as well as a short/long term severe problem for end users.

Advancement flaps are frequently used for nasal reconstruction following skin cancer excision [30]. The nasal subunits – nasal sidewalls, tip and dorsum – along with adjacent facial cosmetic units such as the medial cheeks, glabella and forehead, can be used as donor sites [30-32]. The adequacy of the tissue reservoir in the flap donor area and the alignment of the final sutures with skin tension lines or facial cosmetic units are important considerations when choosing the appropriate advancement flap for nasal defect reconstruction [30, 33].

When it comes to reconstructing the nasal region, both functional and cosmetic considerations are essential to properly repair the nasal defect and restore the normal appearance of the central facial structure [34]. Cheek advancement flaps, despite their complexity in restoring the nasal contour, offer a one-step approach that supplies matched, mobile, and highly vascularized tissue for the reconstruction of nasal defects within natural creases [34]. In our case, an advancement flap was designed to reconstruct the primary skin defect on the left nasal sidewall following excision of a skin tumor, with the cheek serving as the donor site. The final outcome aligned with the patient's facial cosmetic units, resulting in an aesthetically pleasing result.

The intake of potentially polycontaminated medications such as metformin, losartan, hydrochlorothiazide, nifedipine and metoprolol could, in practice, be viewed as a simultaneous polycarcinogenic exposure. Over time, this may lead to the accumulation of carcinogens, potentially resulting in the generation of multiple keratinocyte tumors in UV-exposed areas, within the context of gradual metabolic reprogramming of the future tumor cell. These areas are specifically determined by the likely phototoxicity induced by the nitrosamines [10, 26-27].

In future follow-ups, it would be beneficial to conduct analyses that compare: 1) the availability and precise concentration of specific drug classes in each batch, as indicated on the packaging and certain publicly available sites, and 2) the subsequent development of specific cancer types, particularly keratinocyte cancer.

For this purpose, it is essential to accurately test and formally document phototoxicity in relation to all identified nitrosamines and their derivatives present in medications. This includes assessing their bioavailability before and after metabolism in both blood and skin, as well as the presence of their DNA adducts in lesional skin.

Comparative analyses of nitrosamine-induced gene mutations – such as those affecting the RAS oncogene and/or p53 – and those associated with skin cancers, including basal cell and squamous cell carcinomas, suggest that nitrosamines could be also considered a probable key factor, serving as a unifying pathogenetic element in the development of these cancers [35].

Last but not least, the world and investigators record a heterogeneous, but now officially published, incidence of non-melanoma skin cancer after taking hydrochlorothiazide, for example, in heterogeneous geographical regions [36]. Unfortunately, these follow-ups also remain once again blind to the potential or actual contamination of the drug in question with phototoxic and genotoxic carcinogens, the so-called nitrosamines [36]. In practice, the problem of so-called sporadic unregulated or regulated contamination in a given geographical region is avoided [37]. By this stereotype of shifting the focus or not addressing topics of significant global health importance, the persistent availability of carcinogens in drug products is reinforced, which subsequently guarantees the sky-rocketing incidence of keratinocytic cancer over the years (but not only).

CONCLUSIONS

The fact that current research papers from 2024 (published in PUBMED/MEDLINE) concerning the determination of nitrosamine concentrations in drugs such as rifampicin, champix, famotidine, nizatidine, atorvastatin, bumetanide, itraconazole, diovan, enalapril, propranolol, lisinopril, duloxetine, rivaroxaban, pioglitazones, glifizones, cilostazol, and sunitinib, is growing [38], is indicative of a namely for: The growing acquired awareness in the scientific community of the role of drug-initiated nitrosogenesis/photo- nitrosocarcinogenesis/oncopharmacogenesis and the metabolic reprogramming of the tumor cell with respect to the pathogenesis of skin cancer.

The formalisation of the actual concentrations of nitrosamines and their derivatives in drugs, albeit at concentrations that regulators and manufacturers believe are acceptable, will be able to demonstrate and prove once again the importance of metabolic reprogramming for skin cancer or that: the intake of a cocktail of (photo)carcinogens and/or their genotoxic derivatives/NDSRIs in the context of polymedication/polycontamination, is an undisputed generator/cofactor for skin cancer as well as its frequent recurrence (especially with prolonged intake/analogous to the patient we presented).

In all likelihood or logically considered, this is also the only reason that causes regulators/manufacturers not to formalize these concentrations on drug packaging: the preservation of the secrecy of cancer generation or the preservation of a prescription, which has functioned and still functions for decades in the form of unofficial forced non-alternative at present intake.

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