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CASE REPORT

MELOLABIAL ADVANCEMENT FLAP FOR HIGH-RISK BCC NEAR THE MEDIAL EYE ANGLE: PHOTOTOXICITY/ PHOTOCARCINOGENICITY TRIGGERED BY NITROSAMINES IN THE POLYMEDICATION AS THE MAIN CAUSE OF KERATINOCYTE CANCER DEVELOPMENT AND PROGRESSION

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Abstract. *The enigma that lies behind the concept of drug-mediated phototoxicity/ – carcinogenicity remains exciting, as well as not fully elucidated. Nitrosamines remain one of the few reasonable, according to a number of authors, even the only currently directly responsible explanation for this mystery. The phototoxicity of most of the nitrosamines is a known nonspecific characteristic of them, established as far back as 1972, but also confirmed recently in the scientific literature: phototoxic and genotoxic nitrosamines are present and distributed in medicines worldwide and as of 2024 (nitrosomorpholine in molsidomine for example). This fact could also be seen as largely determining/structurally defining the global incidence of skin cancer, especially in the context of polymedication and polycontamination (with phototoxic/genotoxic mutagens). Hand in hand with UV radiation, these contaminants also lead to overlapping mutations (RAS/p53), which is a good indication of their possible synergistic action in relation to the potentiation of skin carcinogenesis. Nitrosamines and solar radiation are among the factors that have been identified as the initiating phase of carcinogenesis, mainly affecting cutaneous tumours. This is why the polypharmacy could also be considered a determinant of the incidence of cancer-based on permissive regimens for photocarcinogens in drugs. On this occasion, we report on another patient taking 3 heterogeneous classes of drug preparations, two of them catalogued as potentially contaminated in the FDA list of 2024 for carcinogens/nitrosamines: 1) bisoprolol and propafenone, and the 3rd drug: rosuvastatin. The last one is available as nitroso-rosuvastatin but is not catalogued by the regulators in their lists for preparations containing nitroso compounds with defined actual/potential carcinogenic potency. Dermatosurgical management in the form of a melolabial advancement flap was performed, and an optimal aesthetic result was achieved.*

Key words: *melolabial advancement flap, BCC, keratinocyte cancer, drug-related Nitrosogenesis, Phototoxicity, Photocarcinogenicity*

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INTRODUCTION

The problem associated with the generation of cutaneous tumors in the context of photocarcinogenesis is precisely the substances that generate or potentiate the photosensitivity and phototoxicity induced by both UVA and UVB light [1]. Phototoxicity was also identified as a nonspecific property of nitrosamines since 1972 [2]. Recent scientific studies have demonstrated the presence of photo- and genotoxic nitrosamines in ubiquitously distributed drugs [3-5] and bring to the focus or forefront the dilemma: do the other nitrosamines identified in drugs also possess the properties of photo- and genotoxicity (before/after their metabolisation)? Is their bioavailability in skin and blood sufficient to induce this type of reaction? And does this potentiate photocarcinogenesis further in the context of systemic contaminated drug intake? Is nitroso-photocarcinogenesis a substantial part of cutaneous carcinogenesis?

Starting from this (hypo)thesis, we have launched a series of our observations linking the intake of a heterogeneous type of potentially nitrosamine-contaminated drugs (according to the FDA list) [6] to the generation of keratinocyte cancers localized in areas exposed to solar radiation.

We present a consecutive patient taking propafenone, bisoprolol, and rosuvastatin who subsequently developed a tumor formation near the medial orbital angle, surgically removed by melolabial advancement plasty. The role of drug-mediated skin cancer nitrosogenesis or so-called Photo nitroso carcinogenesis/ oncopharmacogenesis [7, 8] is discussed.

CASE REPORT

A 71-year-old female presented to the dermatology department with a primary complaint of a tumor formation beneath her left eyelid, first noticed approximately one year prior to the consultation, with notable growth over the past 4-5 months.

The patient reported medical history of arterial hypertension, Hashimoto's thyroiditis, gout, and hypercholesterolemia. She has been on systemic therapy with lacidipine 4 mg twice daily, propafenone hydrochloride 150 mg twice daily, bisoprolol fumarate 10 mg once in the evening, rosuvastatin 10 mg once daily, all administered for the past 3 years. Additionally, she has been on a regimen of levothyroxine sodium for the past 10 years.

The patient requested physical evaluation, and a further therapeutic approach to be established. Routine blood tests were conducted with no abnormalities.

The dermatological examination revealed a nodular tumor formation with an uneven surface, covered by a hemorrhagic crust and displaying visible teleangiectasias located beneath the left eyelid (Figure 1). The formation was suspected of basal cell carcinoma. Additionally, numerous seborrheic keratoses were observed over the whole body. Enlarged lymph nodes were not palpable.

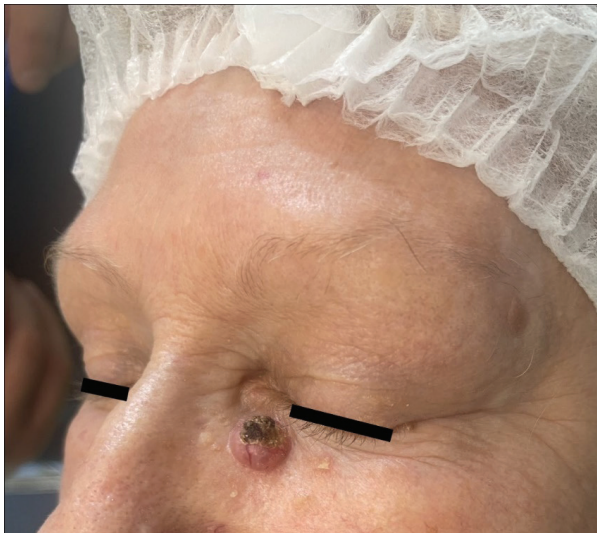

Fig. 1. A nodular tumor formation with an uneven surface, covered by a hemorrhagic crust and displaying visible teleangiectasias, located beneath the left eyelid

The patient was recommended surgical excision under local anesthesia with lidocaine 1%. The tumor formation located beneath the lower left eyelid was removed with an oval excision, maintaining a 4 mm safety margin (Figure 2).

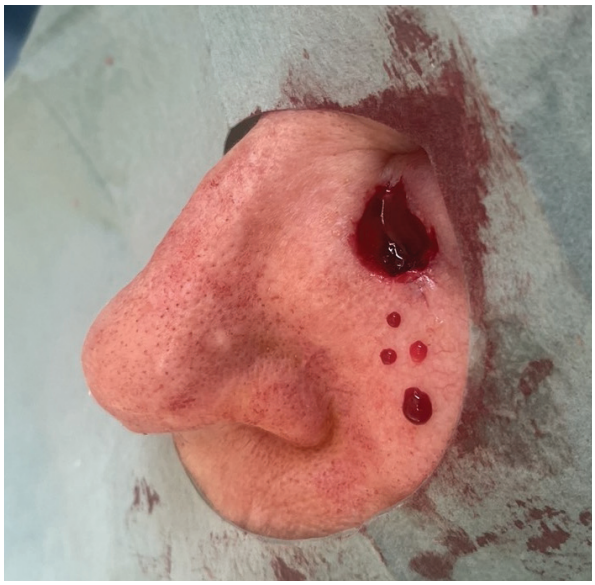

Fig. 2. Intraoperative view: Primary wound defect after elliptical excision of a tumor formation located beneath the left lower eyelid

Hemostasis was performed. Due to the complexity of the primary wound defect, closure with single interrupted sutures or allowing secondary healing were not suitable, as this could result in lower eyelid ectropion or an aesthetically displeasing result. To avoid these complications, the melolabial rotation flap technique was employed for reconstruction. A caudal incision was made at the primary defect, extending to the junction of the nasal sidewall and cheek, terminating just millimeters above the left alar sulcus. The second incision was made perpendicular to the caudal incision, extending to the midface. The melolabial flap was carefully undermined and rotated medially to cover the primary defect, ensuring proper alignment while maintaining the blood supply (Figure 3). The secondary defect was closed with single interrupted sutures (Figure 4). Daily wound dressings with povidone-iodine were made.

The histopathological evaluation showed BCC T1N0M0R1. Active observation and re-excision, if necessary, were recommended due to the presence of tumor cells reaching one resection line. The postoperative course was uneventful.

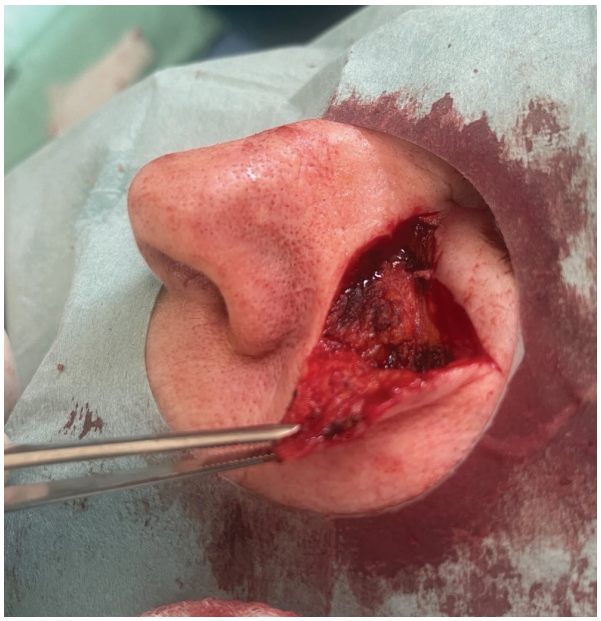

Fig. 3. Intraoperative view: Secondary wound defect: melolabial advancement flap technique

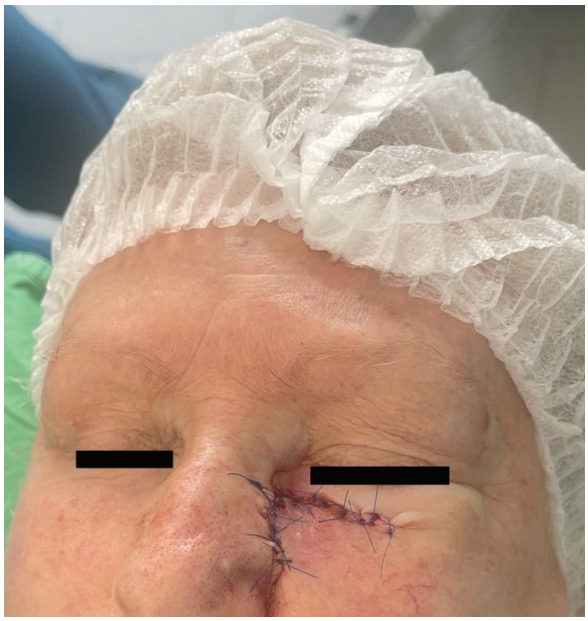

Fig. 4. Intraoperative view: Closure of the secondary wound defect with single interrupted sutures

DISCUSSION

The links between the intake of certain drugs and the development of particular cancer could also be explained indirectly, interactively or sometimes – simply through non-standard analyses and interpretations, similar to the postulate: “All roads lead to Rome”.

The reason for this divergent approach could also be explained by the unconventional, currently unexplained behaviour of regulators and manufacturers, who categorically refuse to formalise the presence of up to several (potentially carcinogens/mutagens (singly or simultaneously) in drugs worldwide [6]. These carcinogens are also known as hepatotoxic, genotoxic and phototoxic substances [2-5].

One way to indirectly identify a problematic factor or, for example, a carcinogen/phototoxic substance, could be explained in the search for correlations between 1) concomitant intake of one or more of one drug (combined drug intake) to 2) potentially nitrosamine-contaminated preparations (according to the FDA list or other national list, such as the Australian list/Health Ministry for example) [6, 9], which intake to be associated with 3) the subsequent generation of skin tumors (whether melanoma or keratinocytic) that are 4) localized predominantly in areas, exposed to sunlight.

There is no shortage of such analyses in the PubMed/MEDLINE literature, and in serious quantities: some of them focus on the concurrent intake of several potentially contaminated drugs and the subsequent development of a particular form of skin cancer, keratinocytic for example [10-12], while others are more related to the development of a particular skin tumor/multiple ones (epithelial, melanoma, atypical fibrosarcoma, dermal pleomorphic sarcoma, etc.) after the intake of only a given group of drugs or one particular drug [13-15].

The unifying or indicative link in these 2 forms of medication intake could be simply the presence of a given photo- and genotoxic substance, also known as nitrosamine or NDSRIs [2-5]. Or substances that are actually present in drugs but remain known only to regulators [6, 9].

The development of a monomorphic clinical picture (keratinocyte skin tumors, melanoma, etc.) according to the criteria mentioned above or just mentioned would help to identify a currently forgotten quality of many nitrosamines by the scientific community – their phototoxicity [2-5], which for the moment remains in the shadows of deep forgetfulness.

The uncertainty about the somewhat divergent scientific data on the incidence of a given form of skin cancer (including that of basal cell carcinomas after intake of potentially contaminated drug products) could be explained by the different or so-called uncontrolled/ controlled contamination in again different geographical regions. This issue could be cleared quickly with the formalization of the exact type and concentration of the so-called nitrosamines in the preparations, which should not be problematic considering their only "potential human carcinogenic potency" [6, 9].

Propafenone is a drug with a potential carcinogenic potency of 2, according to the FDA list [6]. While monomedication with nitroso-propafenone could be a potential risk factor for the development of lethal metastatic melanoma [16], administration of propafenone in combination with other potentially contaminated drugs has been pathogenetically associated with the development of multiple epithelial tumors [17, 18].

An analogous direction could be the considerations towards rosuvastatin or nitroso-rosuvastatin [19], which has not yet been announced as a drug with potential carcinogenic potency in the 2024 FDA list [6]. However, according to recent literature data, the combined intake of nitroso-rosuvastatin with other potentially contaminated drugs of a heterogeneous class could be associated with the generation of melanomas/dysplastic nevi (20) as well as with that of keratinocyte cancers [21]. A link here could again be nitrosamine-mediated phototoxicity [22].

New scientific data have linked nitroso-bisoprolol intake in the context of polycontamination of multimedication with subsequent development of epithelial skin tumors, including basal cell carcinomas [10, 11, 23].

In practice, and with real contamination proven, the intake of propafenone, bisoprolol, and rosuvastatin, could be the intake of a cocktail of 3 to 6 carcinogens, also known as nitrosamines, with heterogeneous carcinogenic potency: Propafenone-2 (100 ng/day), Bisoprolol-4 (1500 ng/day), and Rosuvastatin, which is not currently catalogued in the FDA list but is likely to be soon [6].

Drug-mediated nitrosogenesis is not a myth but remains a reality due to its prominent place on the pedestal of carcinogenesis due to the presence of nitroso-photo mutagens in drugs, also known as nitrosamines [24].

Prolonged intake of these drugs, even after successful surgical interventions, could lead to locoregional recurrences and/or new skin tumors [7, 17, 18, 22, 23].

Surgical manipulations in the facial area are a serious challenge not only for every dermatosurgeon, but also for the patients themselves. The reasons for this are the postoperative results, which do not always meet the expectations of the patients/ but also of the physicians. Side effects range from facial asymmetry, ectropion, infection, and keloids to the need for reoperations or additional treatment.

High-risk areas such as the medial orbital angle are also extremely dangerous due to their anatomical features, such as 1) proximity to the angular veins and inferior nasolacrimal canal. The inferior lacrimal canal could be discontinued during this type of surgery, which could be associated with a subsequent serious dose of discomfort if the compensatory capabilities of the superior lacrimal canal are organic or if it is also damaged (for this or any other reason).

The correct level of deep excision of the skin that is planned to be repaired is also important: 1) when deeper areas within the primary excision are involved, there is a risk of permanent nerve damage or ischaemia due to vascular damage, whereas 2) when more superficial excision is undertaken, there is a risk of cicatrization due to tension at the resection edges.

CONCLUSIONS

In conclusion, we presented a patient with a serial epithelial skin tumor localized near the eye and discussed the possible role of drug-mediated photo nitrosogenesis/photo toxicity in the context of polymedication and polymorbidity.

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