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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

**Медицинские новости Грузии**

საქართველოს სამედიცინო სიახლენი

**GEORGIAN MEDICAL NEWS**

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**GMN: Georgian Medical News** is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

**GMN: Медицинские новости Грузии -** ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

**GMN: Georgian Medical News –** საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

**WEBSITE**

www.geomednews.com

## К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

**При нарушении указанных правил статьи не рассматриваются**.

## REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.**

## ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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# EDUCATION FROM DERMATOLOGISTS: THE SIMULTANEOUSLY DEVELOPMENT OF 16 KERATINOCYTIC CANCERS AFTER USE OF METFORMIN IN COMBINATION WITH LOSARTAN/ HYDROCHLOROTHIAZIDE, METOPROLOL AND NIFEDIPINE- IMPORTANT LINKS TO DRUG RELATED (PHOTO)-NITROSO-CARCINOGENESIS AND ONCOPHARMACOGENESIS

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## Abstract.

Oncopharmacogenesis and Drug-Induced Skin cancer related Nitrosogenesis are newly introduced concepts in the medical literature that owe their genesis or presence to the carcinogens/ mutagens, also known as nitrosamines/NDSRIs, which are present in a heterogeneous class of drugs. The contribution to the origin of these 2 concepts is entirely due to 1) the functions and efficacy of FDA in terms of control and identification of these carcinogens, and 2) the establishment of clinicopathological correlations by the dermatologists, occurring during drug intake.

According to recent FDA data, the concentration of NDMA in just one metformin tablet could be up to more than 5-fold increased. The intake of 3 to 6 tablets per day should result in a carcinogen intake that is 15 to 30 times elevated within the day and within the monomedication alone. It is these circumstances that paraphrase/ ″betonate″ concepts such as Onco-Pharmacogenesis and Drug-mediated Nitrosogenesis of skin cancer. Although not officially declared, these mutagens are present and have been in forced tolerance mode for the last 30-40 years. And after their intake, multiple cancers have been found to develop.

The concomitant use of other nitrosamine-contaminated drugs such as losartan/hydrochlorothiazide, metoprolol and nefidipine should certainly not be surprising when it could also be associated with the development of exactly 16 keratinocytic tumours as in the case presented by us.

Recent evidence in medical literature has linked the nitrosamine N-nitrosomorpholine (NMOR) with the direct development of its subsequent mutagenic action in rodents following irradiation with UVA. This fact leaves open the question of the potentially available photocarcinogenic action of the other nitrosamines in humans found in medicinal preparations. This is what necessitates a clarification of the concept of Photo-Nitroso-Carcinogenesis/ Oncogenesis in humans and its relationship to skin cancer.

The overlap of the mutational patterns of some of the nitrosamine-induced mutations in target genes such as p53 and RAS oncogenes, with those of UV light-induced mutations - or practically the same ones mentioned above, suggest a possible significant role of the Drug-Induced Photo-Nitroso-Carcinogenesis of keratinocyte cancer in the context of Onco-Pharmacogenesis. Future analyses should focus on elucidating the photocarcinogenic effect of nitrosamines in drug preparations and differentiating Skin cancer Nitrosogenesis from ″pure″ Photo-Carcinogenesis and Nitroso-Photo-Carcinogenesis.

The localization of the tumors in the area of the UV-exposed sites within the potential/actual contamination of the 4 preparations (simultaneously) in the described patient are indicative of a possible pathogenetic influence in the context of the already mentioned Nitroso-(Photo)carcinogenesis. Polycontamination of polymedication remains a so far unresolvable problem.

**Key words.** Nitroso/Photocarcinogenesis, Oncopharmacogenesis, BCC, SCC, Nitrosamines, Metformin, NDMA, losartan/hydrochlorothiazide, nifedipine, metoprolol.

## Introduction.

Combined intake of a heterogeneous class of drugs within the framework of the recently established contamination with nitrosamines/NDSRIs by control organs in the face of FDA and EMA [1,2], could prove risky in terms of the development of single or multiple keratinocytic cancers [3-5]. Nitrosamines are some of the most potent carcinogens for human DNA, and this is true for certain representatives of them with full force [6]. Despite this previously undeniable fact, enforced tolerance regimens for nitrosamines and their nitroso derivatives in drugs remain, and elimination of the latter is not a priority for regulators and manufacturers.

Specific nitrosamines in tobacco have been shown over the years to have carcinogenic/genotoxic effects on the p53 genome regulator and in RAS oncogenes [6]. The genes affected appear to be genes in which mutations are directly responsible for generating keratinocytic cancers (basal cell carcinoma and squamous cell carcinoma of the skin), but not only [7-9]. The somewhat overlapping mutational patterns between 1) UV radiation-induced mutations with those of 2) those induced by some members of the nitrosamine family [6] should be at least alarming with respect to future elucidation of the mutational pattern/genotoxic action of nitrosamines in drugs.

This fact should lead not only to a clarification of the role of nitrosamines and their pathogenetic mutagenic/ carcinogenic/ genotoxic effects, but also to an accurate indication of their actual, rather than potential or hidden, presence on the packaging of medicinal products. The lack of this formalisation to date remains to be highly concerning and, in all likelihood, there are reasons for this.

Some of the nitrosamines are also potent photocarcinogens [10]. This demonstrates, albeit indirectly, the potential link

between Nitroso-Photocarcinogenesis of skin cancer in the context of onco-pharmacogenesis/Carcinogenesis, provided that the photocarcinogenic effect of the potential carcinogens/mutagens in question present in medical devices is demonstrated [11,12].

The dilemma remains: Is the phototoxicity in the drugs due in whole or in part to the nitrosamines and their nitroso derivatives present but not yet reported?

In the context of the above, a number of observations have been initiated in recent years on 1) the intake of potentially/actually contaminated drugs (as per the 2023/2019 FDA list) and 2) the subsequent simultaneous or stepwise occurrence of single or multiple skin cancers. As should be noted, it is remarkable that the severity of the clinical presentation corresponds once again with the number of patients taking drugs declared as potentially/ actually contaminated in the FDA list from 2019 and 2023 [13-15].

A patient who developed 16 keratinocytic tumors during this admission is presented and the relationship between Nitrosogenesis, Photo/Nitroso-Carcinogenesis and Onco-Pharmacogenesis of skin cancer is commented. Concepts that are related to each other are newly introduced in the medical literature and cannot be ignored, as in all likelihood they will have to prove their clinical relevance in the near or more distant future [11,12].

## Case report.

A 74-year-old male presented to the dermatology department with primary complaints of a tumor-like formation in the area of the right lower eyelid, which he reported noticing about a year or two prior to the consultation.

The patient reported a history of prostatectomy, anemia, arterial hypertension for 29 years, atrial fibrillation and flutter, non-insulin dependent (type 2) diabetes mellitus for 32 years with neurological complications and diabetic polyneuropathy.

For his arterial hypertension he has been taking losartan potassium/hydrochlorothiazide 50mg/12.5mg 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 in the morning for the past 3 years. For his diabetes he has been taking glimepiride 3 mg once in the morning for 15 years; along with metformin hydrochloride 850 mg three times a day for 15 years. Additionally, he takes pentoxifylline 400 mg once in the evening and thioctic acid once in the morning both administrated for 20 years.

The patient had a previous history of several cutaneous malignancies and had undergone 16 surgical interventions to remove them during the last 3-4 years. In 2020, he underwent surgical removal of squamous cell carcinomas in the right and left cheek area, as well as in the nose area. In February 2021, four squamous cell carcinomas were removed in the right temporal region, right lower eyelid, right facial and in the right auricle areas. In October 2021, four squamous cell carcinomas were removed: two located in the left auricle, one in the left auricle cartilage, and one in the right facial area. Additionally, one basal cell carcinoma in the left facial area was removed. In 2022, tumor formations in the left temporal, right, and left preauricular regions were surgically removed, resulting in moderately differentiated squamous cell carcinomas. In February 2024, in the right temporal region a well differentiated (G1) squamous cell carcinoma was removed, staged T1N0M0.

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

Routine blood tests were performed, resulting without abnormalities except for the hemoglobin level (HGB) – 112.0 g/L (normal range 138-172 g/L) and creatinine– 148.5 μmol/l (normal range 61.9 – 114.9 μmol).

The dermatological examination showed a cauliflower-like tumorous formation encompassing the entire lower eyelid and extending to a portion of the nose (Figure 1). The tumor involved the full thickness of the eyelid, including the underlying conjunctiva and all components of the lacrimal apparatus. The surrounding skin appeared atrophic, patchy, and hyperemic (Figure 1). Lymph nodes were not palpable.

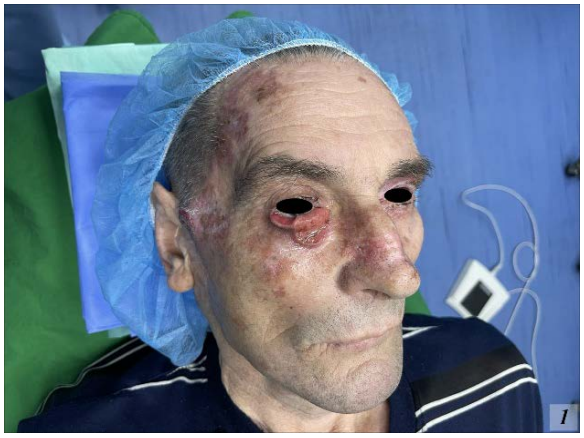


***Figure 1.*** *Cauliflower-like tumorous formation encompassing the entire lower eyelid and extending to a portion of the nose. The tumor involves the full thickness of the eyelid, including the underlying conjunctiva and all components of the lacrimal apparatus. The surrounding skin appeares atrophic, patchy, and hyperemic. Preauricular right localized tumor formation suggestive of epithelial skin tumor.*

Based on the patient's history and the physical examination, the lesion was clinically suspected for squamous cell carcinoma. Surgical removal under local anesthesia was recommended.

The lesion located in the right lower eyelid was surgically removed, involving the entire length and depth of the eyelid by advancement flap from the neighbourhood (Figure 2a-c). The tumorous formation was resected in clinically healthy tissue and sent for histopathological evaluation, revealing a poorly differentiated (G3) squamous cell carcinoma, staged T1N0M0, with 10% involvement of one resection margin. Tarsal reconstruction was conducted using deep fixation sutures, followed by layer-by-layer suturing of the surrounding area using absorbable and non-absorbable 4/0, 5/0, and 6/0 sutures (Figure 2d). The postoperative period went without any complications (Figure 3). Three drops of neomycin sulfate/polymyxin B sulfate/ dexamethasone suspension four times daily in the right eye and gentamicin cream two applications twice daily in the right lower eyelid were prescribed. The histopathological verification was indicative for Low-differentiated G3 squamous cell carcinoma of the lower right eyelid T1N0M0R1/ with 10% involvement of one of the resection lines.

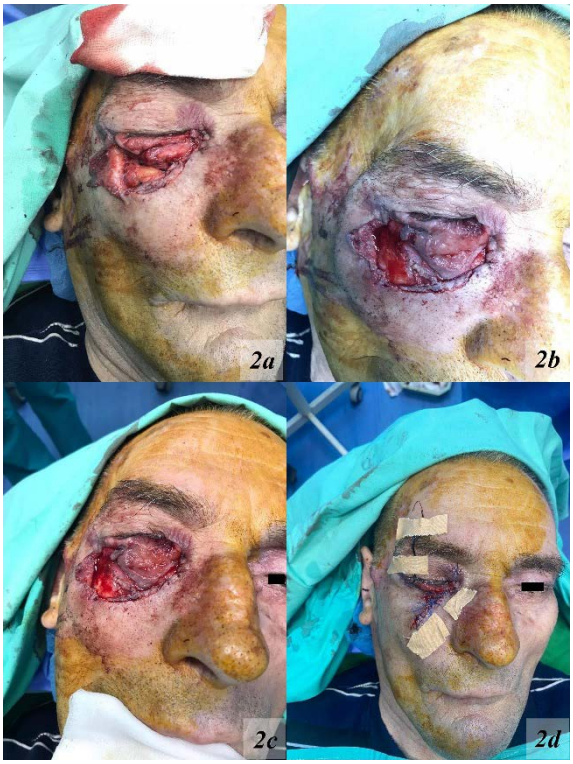


***Figure 2.*** *Intraoperative view: The tumorous lesion was surgically removed, involving the entire length and depth of the eyelid (a-c).*
***2a-2c:*** *advancement flap from the neighborhood, with the transposed flap directed in the direction from the temple to the nose.*
***2d:*** *Tarsal reconstruction was conducted using deep fixation sutures, followed by layer-by-layer suturing of the surrounding area using absorbable and non-absorbable 4/0, 5/0, and 6/0 sutures. Postoperative photo immediately after the intervention.*


***Figure 3.*** *Postoperative view after 14 days. The keratinocytic tumor with preauricular localization has completely healed after the surgical intervention/ surgical plastic. The lesion involving the lower eyelid was planned for reoperation to clear one resection line and achieve a better aesthetic result.*

Reoperation and Reconstruction of the lower eyelid was planned as well as surgical removal of the tumor affecting the left auricle.

The second lesion was localized preauricularly on the right and was again suspicious for cutaneous squamous cell carcinoma (Figure 1). The lesion was surgically removed by elliptical excision, and due to the inability to close the defect by extension flap, the following was performed: 1) partial closure of the distal part of the defect by extension flap/several sutures, followed by 2) formation and transposition of a flap in the proximal direction to adapt the resection edges to the opposite edge of the defect. This is followed by underming surgery and a stepwise adaptation of the edges of the defect according to the lowest point of resistance in order to achieve an optimal final cosmetic effect (Figure 3). Histopathological verification was with evidence of a highly differentiated G1 squamous cell carcinoma, and staging was determined as G1T1N0M0, clear resection lines.

## Discussion.

Until recently, polymorbidity was generally thought to be one of the important causes/preconditions for the generation or potentiation of cancer worldwide, within the context of ″universal body damage″ [16-18].

Part of the opinion of certain groups of experts is that polymorbidity and polymedication could also have a negative effect on tumor biology in general [19]. These specialized, expert opinions unfortunately do not specify or detail how polymedication could negatively affect carcinogenesis (to date). Logical explanations were lacking. Until recently.

Current state-of-the-art and innovative single patient cases/ case series follow-up studies in the global literature are indicative of a real and significant association available between the intake of heterogeneous (nitrosamine contaminated according to the 2019/2023 FDA lists) mono- or polymedication and the subsequent development of keratinocytic cancer [3,4,5,13-15].

Large-scale retrospective follow-up studies from America and Europe found also a significant association between the intake of (potentially FDA-contaminated) medication with sartans and hydrochlorothiazide and other diuretic-type drugs and the subsequent occurrence of keratinocytic tumors [20,21].

A German collective found an association between the intake of thiazide diuretics/ACE inhibitors and the development of cancer in areas exposed to direct UV radiation [22].

However, none of the aforementioned papers address 1) the contamination of the medication with nitrosamines [20-22], and 2) their potential photocarcinogenic/genotoxic effects (of some of the nitroamines) [10], as possible important cofactors in the potentiation of keratinocytic cancer [3-5].

The question remains: are nitrosamines potent photocarcinogens, enhancing the action of UV radiation as well? Or does ultraviolet radiation exert its photocarcinogenic action mainly in the presence of nitrosamines (in one form or another)?

In practice, it appears that the most reliable dermatological schools/ scientific groups around the world link the development of skin cancer to the intake of drug groups declared by regulators as potentially contaminated with nitrosamines?

But individually, or all together, everyone denies this link?

The reasons for this refusal to formalize the objective truth could not be difficult to interpret, because this act of inactivity, is precisely the very confirmation of the real situation: ″You take carcinogenic ingredients (nitrosamines) not yet formalized in the drug content and later or shortly after that you develop skin cancer?″

This dilemma could be quickly resolved when: formalizing the ingredients on the packaging of the medicinal product, in order to study their carcinogenic, mutagenic, genotoxic or photocarcinogenic action in the framework of Onco/ Pharmacogenesis and Nitroso- Photo-Carcinogenesis [11,12].

A reality that turns out to be rather a myth or a parallel reality of the absurdities.

One of the upcoming or inevitable future tasks for clinicians, regulators, and manufacturers remains the elucidation of Nitroso-Photo-Carcinogenesis concerning each individual nitrosamine identified in the drugs described to date by the FDA as potentially/actually contaminated with carcinogens [11,12].

Metoprolol and nefidipine are known in the form of nitroso compounds [23,24], while also being listed by the FDA as potentially/actually contaminated or nitroso preparations having a defined carcinogenic potency of 4 and 5 [1].

Hydrochlorothiazide and losartan have carcinogenic potencies of 4 and 2 [1,2]. The concomitant intake of these 4 drugs (with potential carcinogenic potencies of 2 to 4 and 5) [1,2] is further complicated by the concomitant intake of metformin, potentially contaminated with NDMA (class 2 carcinogenic potency) [25,26].

Is it surprising to anyone that the intake of 5 different types of carcinogens simultaneously over a 15–20-year period could lead to multiple keratinocytic tumors?

One should not forget the circumstance concerning a recent article published in the Journal of the American Academy of Dermatology and Venereology linking the monomedication with hydrochlorothiazide and the subsequent development of keratinocytic cancer/ nonmelanoma skin cancer and melanoma [27]. The article does not thematize 2 extremely important points: the presence of potential/possible polymedication in patients presented and 2) potential polycontamination with nitrosamines, some of which-possibly possessing analogous to the recently shared evidence of an available photocarcinogenic, genotoxic effect [10].

Regardless of which drug they are present in, nitrosamines are and remain potent human carcinogens capable of generating heterogeneous forms of skin cancer [28].

NDMA-contaminated metformin, in the context of polymedication, has recently been described as a trigger of multiple keratinocytic cancers/ basal cell carcinoma, etc., arising specifically in combination with losartan and ACE inhibitors, as well as antidepressants [28].

A similar paper commented on the intake of potentially nitrosamine contaminated (NDMA?) metformin, linking the rapid progression of the tumor lesion to the intake of the drug [29].

Although few at present, articles are indicative that potential contamination of mono or polymedication, correlates on the one hand with 1) the severity of clinical findings or the number of keratinocytic tumors [3-5,28,29], and on the other hand with 2) the carcinogenic potency of potentially or actually affected drugs in the context of mono and polymedication [1,2,25,26].

Future analyses should focus on 1) clarifying the photo-carcinogenic potency of the nitrosamines themselves relative to the declared one (phototoxicity) concerning the pure substance to date, and 2) on accurately cataloging and formally declaring the availability of these carcinogens in each drug.

Do the mutational patterns of UV-induced changes/gene toxicity overlap or not with those caused by nitrosamines? Are the nitrosamines contained in the drugs potent photocarcinogens? The answers to these questions are more than a necessity that determines the incidence of keratinocytic cancers in the context of polycontamination and Nitroso/ Pharmaco/ Oncogenesis, Photo-Nitroso- Pharmaco-oncogenesis of skin cancer.

Metformin, contaminated with NDMA, is a fact that is undeniable, as the contamination of any one tablet can vary within the mono- or combination preparations from 0 to 156.8 ± 32.8 ng/tablet initially and increases to 25.4 ± 5.1 to 455.0 ± 28.4 ng/tablet after 3 months of exposure to conditions of use [30,31]. The fact that the acceptable daily intake of NDMA, or so-called ADI, is 96 ng/day should not be overlooked [31]. That is, the FDA has found up to a 5-fold elevated level of the carcinogen in a single tablet [31]. In practice, three times the intake of actually contaminated tablets (in this scenario and consistent with the patient we described) could calculate a contaminated metformin intake with doses exceeding up to 15 times the maximum tolerable intake dose of the carcinogen. In parallel, the patient was taking 3 other potentially/actually contaminated medications according to the FDA list for carcinogen-contaminated drugs: losartan/hydrochlorothiazide, nifedipine, and metoprolol (see case report data).

The way out of this ″awkward situation″ of creating compulsory intake of polycontaminated preparations could only be limited or eliminated by the establishment of national regulatory authorities that would conduct strict multiple, consistent, and permanent control of each batch and for each class of medication. Data must be publicly disclosed and accessible to end consumers, physicians, regulators, and manufacturers in order to ensure the maximum security of each nation's health integrity. To date, there is a definite lack of a solution to the issues surrounding the use of contaminated polymedication in polymorbid patients. Regulators and manufacturers have not found a resolution on how the daily intake of carcinogens in polymorbid patients (with polymedication) can be limited or eliminated completely.

The clinicopathologic correlations within this intake and in the case series we have presented are indicative of how the potential intake of polycontaminated agents could be pathogenetically associated with the subsequent development of 16 keratinocytic tumors.

## REFERENCES

1.https://www.fda.gov/regulatory-information/search-fda-guidance-documents/updated-information-recommended-acceptable-intake-limits-nitrosamine-drug-substance-related

2. https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan
3. Tchernev G. Multiple Keratinocytic Cancers After Enalapril/Losartan Intake: Potential Links To Drug Mediated Nitrosogenesis/Carcinogenesis: Melolabial Advanced Flap And Undermining Surgery As Optimal Therapeutic Approach. Georgian Med News. 2023;344:196-199.
4. Tchernev G. Nitrosamine Contamination Within Cardiac Multimedication - Sartans (Valsartan), Calcium Channel Blockers (Amlodipine And Nifedipine), And Antiarrhythmics (Propafenone) As A Significant Factor In The Development And Progression Of Multiple Keratinocytic Cancers: Advancement Rotation Flap For Keratoacanthoma Of The Upper Lip And Undermining Surgery For Bcc Of The Shoulder As An Optimal Dermatosurgical Approach. Georgian Med News. 2023;342:152-155.
5. Tchernev G. Nitrosamine Contamination Within Cardiac Multimedication - Sartans (Valsartan), Calcium Channel Blockers (Amlodipine And Nifedipine), And Antiarrhythmics (Propafenone) As A Significant Factor In The Development And Progression Of Multiple Keratinocytic Cancers: Advancement Rotation Flap For Keratoacanthoma Of The Upper Lip And Undermining Surgery For Bcc Of The Shoulder As An Optimal Dermatosurgical Approach. Georgian Med News. 2023;342:152-155.
6. Stanfill SB, Hecht SS, Joerger AC, et al. From cultivation to cancer: formation of N-nitrosamines and other carcinogens in smokeless tobacco and their mutagenic implications. Crit Rev Toxicol. 2023;53:658-701.
7. Piipponen M, Riihilä P, Nissinen L, et al. The Role of p53 in Progression of Cutaneous Squamous Cell Carcinoma. Cancers (Basel). 2021;13:4507.
8. Boeckmann L, Martens MC, Emmert S. Molecular Biology of Basal and Squamous Cell Carcinomas. Adv Exp Med Biol. 2020;1268:171-191.
9. Brash DE, Ziegler A, Jonason AS, et al. Sunlight and sunburn in human skin cancer: p53, apoptosis, and tumor promotion. J Investig Dermatol Symp Proc. 1996;1:136-42.
10. 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;893:503721.
11. Tchernev G, Naydekova N, Ivanov L, et al. Enigmatic lessons from Dermatologists: Pharmaco-Oncogenesis and Nitrosogenesis of skin cancer: Facst and controversies. Journal Meditsinski pregled. 2024;60:67-72.
12. Tchernev G, Ivanov L, Todorov I, et al. Basal cell carcinoma development after combined administration of Lisinopril and Tamsulosin: links to Photocarcinogenesis and Nitrosogenesis in the context of Pharmaco-Oncogenesis. Journal Meditsinski pregled. 2024;60:48-54.
13. 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;339:24-32.
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;337:63-67.
15. 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;335:22-25.
16. Sørensen HT. Multimorbidity and cancer outcomes: a for more research. Clin Epidemiol. 2013;5:1-2.
17. Extermann M. Interaction between comorbidity and cancer. Cancer Control. 2007;14:13-22.
18. George M, Smith A, Sabesan S, et al. Physical Comorbidities and Their Relationship with Cancer Treatment and Its Outcomes in Older Adult Populations: Systematic Review. JMIR Cancer. 2021;7:e26425.
19. Panigrahi G, Ambs S. How Comorbidities Shape Cancer Biology and Survival. Trends Cancer. 2021;7:488-495.
20. Nardone B, Majewski S, Kim AS, 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;40:249-255.
21. Schmidt SA, Schmidt M, Mehnert F, et al. Use of antihypertensive drugs and risk of skin cancer. J Eur Acad Dermatol Venereol. 2015;29:1545-54.
22. Mehlan J, Ueberschaar J, Hagenström K, 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;260:2745-2751.
23. Imanishi M, Izawa-Ishizawa Y, Sakurada T, et al. Nitrosonifedipine, a Photodegradation Product of Nifedipine, Suppresses Pharmacologically Induced Aortic Aneurysm Formation. Pharmacology. 2018;102:287-299.
24. Robbiano L, Martelli A, Allavena A, et al. Formation of the N-nitroso derivatives of six beta-adrenergic-blocking agents and their genotoxic effects in rat and human hepatocytes. Cancer Res. 1991;51:2273-9.
25. https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-metformin
26. https://www.tga.gov.au/news/safety-alerts/potential-contamination-australian-metformin-medicines
27. Azoulay L, St-Jean A, Dahl M, et al. Hydrochlorothiazide use and risk of keratinocyte carcinoma and melanoma: A multisite population-based cohort study. J Am Acad Dermatol. 2023;89:243-253.
28. Tchernev G, Kordeva S, Marinov V, et al. Nitrosamines in antihypertensives, metformin and ranitidine as co-factors for melanoma and development of other cancers. Expert group opinion. Port J Dermatol Venereol. 2022;80:332-334.
29. 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;339:24-32.

30. Tchernev G, Kordeva S. Basal cell carcinoma development after use of metformin: potential role of nitrosamines as enhancing factors. Port J Dermatol Venereol. 2023;80:65-68.

31. Dharani S, Mohamed EM, Rahman Z, et al. Patient In-Use Stability Testing of FDA-Approved Metformin Combination Products for N-Nitrosamine Impurity. AAPS Pharm Sci Tech. 2024;25:19.