GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 11 (356) ноябрь 2024

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

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.

GEORGIAN MEDICAL NEWS
No 11 (356) 2024

Содержание:

GEORGIAN MEDICAL NEWS
No 11 (356) 2024

POLYPHARMACY AND CANCER: A NEW VISION FOR SKIN CANCER PATHOGENESIS- PHOTOTOXICITY AND PHOTOCARCINOGENICITY DUE TO NITROSAMINE CONTAMINATION DURING TELMISARTAN/ TAMSULOSIN INTAKE

Tchernev G[1,2], Kordeva S[1], Kirilova H[2], Broshtilova V[3], Patterson JW[4].

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

[2]*Department of Dermatology and Venereology, Medical Institute of Ministry of Interior, General Skobelev 79, 1606, Sofia, Bulgaria.*

[3]*Department of Dermatology and Venereology, Medical Military Academy, Sofia, Bulgaria.*

[4]*Professor Emeritus of Pathology, Department of Pathology, University of Virginia, Charlottesville, USA.*

Abstract.

The toxicokinetics of nitrosamines remain a mystery to this day, though it appears that the role of nitrosamines in potentiating the generation of mutations required for the onset of skin cancer continues to be a significant concern. Nitrosamines are mutagens, genotoxic substances, and mediators of phototoxicity/ carcinogenicity, whose long-term daily usage, in the context of polypharmacy, can result in the parallel appearance of heterogeneous forms of skin cancer: keratinocytic and melanocytic. But a number of clinical observations suggest that it is the nitrosamines that potentiate the multiple occurrences of skin cancer over the years, or recurrences of skin cancer localized in areas exposed to solar radiation.

This article reports the occurrences of keratoacanthoma and multiple actinic keratoses in a patient on systemic therapy with telmisartan and tamsulosin - medications that contain Nitrosamines/ NDSRIs. Successful surgical treatment by modificated advancement flap and cryotherapy was performed. The role of nitrosamines as mediators of phototoxicity in the context of drug-mediated Photo-Nitrosogenesis/ Nitrosocarcinogenesis is discussed.

Contamination of certain classes of drugs with nitrosamines is proving to be more than a serious problem. This problem is fueled on the one hand by the fact that nitrosamines are 1) photocarcinogens (known for decades), but on the other hand, they are also 2) mutagens/carcinogens, genotoxic substances (according to the FDA classification).

The phototoxic effect according to current data is not calculated by the tests provided by the regulators (at least so far), which in practice leads to a miscalculation of the total, cumulative carcinogenic effect in the context of the intake of a contaminated mono or polymedication. The tests could be seen as either largely static, according to some clinical observations- even as categorically insufficient in terms of defining the concept of carcinogenicity in real-world settings (such as the intake of carcinogens with drugs, for example). The processes of carcinogenesis are dynamic, multifactorial and could hardly be characterized by this kind of tests.

New literature evidence finds a disconnect precisely in the determination of carcinogenic activity by assays proposed by regulators such as the Ames test (in bacteria) and the CPCA test in rodents.

An open dilemma remains: since there is no concordance between the mutagenicity test in bacteria (Ames) with that in rodents (CPCA) , what should be their significance in humans?

For this reason, the application of the above-mentioned tests might be seriously limited in the future.

We present a patient with multiple actinic keratoses and an epithelial skin tumor in the scalp area that developed during therapy with Tamsulosin and Telmisartan. We comment on the role of drug-mediated Photo-Nitrosocarcinogenesis/ Oncopharmacogenesis in the background of potential/actual carcinogen contamination.

Key words. CPCA test, Ames test, tamsulosin, telmisartan, keratinocyte cancer, FDA, advancement flap, Nitrosogenesis, Photo Nitrosocarcinognesis, skin.

Introduction.

Concepts such as phototoxicity and photocarcinogenicity appear to be inextricably linked, but unfortunately relatively little is known about their pathogenetic significance concerning skin cancer – including epithelial cancers and melanoma. There remains a number of unanswered questions. Why does a drug cause a phototoxic reaction in one patient but not in another? Is it determined by the body's contact with photocarcinogens present in certain batches of a drug but not in others? Which factors determine the occurrence of photocarcinogens in the body? What are the sources of photocarcinogens, e.g. foods, medicines, or cosmetic products? Which are more dangerous: nitrosamines in medicines or the products resulting from their metabolism? Is a particular nitrosamine metabolized differently depending on how it comes into contact with the human body, e.g. via the skin/skin microbiome, gut flora/ gut microbiome, or liver? Can certain nitrosamines be deposited in the skin without being metabolized and cause phototoxic and/or genotoxic reactions?

The incidence of skin cancer worldwide is skyrocketing! Is this occurring in parallel with polymedication - and, perhaps, poly-contamination?

Of particular interest are the data from as far back as 1972 that define the phototoxicity of nitrosamines as a nonspecific property due to the photodecomposition of their nitroso group after exposure to ultraviolet radiation [1]. In practice, drugs, food, water and cosmetic products are some of the most important prerequisites for human exposure to nitrosamines or their derivatives.

After irradiation with UVA, nitrosamine, also known as nitrosomorpholine, is mutagenic even without the need for metabolic activation in the body [2].

Photoactivated nitrosamine/nitrosomorpholine that comes into contact with the skin could possibly be directly genotoxic or mutagenic to the human organism [2].

To a great surprise, the aforementioned nitrosamine, nitrosomorpholine (NMor), was also found as a contaminant in a preparation for patients with ischemic heart disease, as the concentration of each tablet of the vasodilator molsidomine contained 144% of the toxicologically allowable intake of NMor [3].

The same scientific publication addresses the real contamination of a certain drug from the group of sartans with up to two nitrosamines at the same time: NDMA and NDEA [3].

In turn, NDMA has been shown to be carcinogenic in rodents, inducing tumors of the gastrointestinal tract, liver and kidney [4,5]. Even more intriguing is the fact that the active, methylated metabolite of NDMA – methyldiazonium - is also mutagenic [6]. In practice, the intake of one nitrosamine becomes equivalent to the intake of two mutagens; alternatively, some of the nitrosamines may be poly-carcinogenic [6].

It is interesting that regulators and drug manufacturers permit the presence of nitrosamines in a certain concentration in quite a number of globally distributed drugs [5]. Moreover, the assays used to determine the mutagenic activity of nitrosamines present in these drugs are proving to be problematic, and their relevance at present remains controversial. According to recent data, the Ames test (in bacteria) shows results that do not correlate with those of a test such as CPCA [6]. This could in all likelihood be due to the poly-carcinogenic action of a number of nitrosamines, and the resulting inability or failure to consider their combined action in the context of skin carcinogenesis.

In our previous publications we have presented the clinical data, which do not appear to correspond to those of the regulators and are subject to a particular misinterpretation; namely, that one cannot expect a clear association between mutagenicity in bacteria and in rodents due to their contact with nitrosamines [7,8].

Persistent intake of multiple drugs containing up to several nitrosamines or their derivatives (even for a relatively short period of about 3 years) could be pathogenetically associated with the occurrence of single to multiple cutaneous tumors (especially in the context of poly-contamination with mutagens [7,8].

Further, albeit indirect, evidence for the phototoxicity and genotoxicity of nitrosamines in drugs is the fact that their intake is strongly associated with the subsequent development of melanocytic tumors [9,10], atypical fibroxanthoma, and others that manifest clinically in areas re-exposed to solar radiation [11].

The relationship between the intake of phototoxic substances (such as nitrosamines) in the context of mono or poly-medication over a prolonged period of time, and the development of single or multiple tumours in areas exposed to UV radiation, should not be regarded as coincidental. Moreover, the current lack of reliable mutagenicity tests lends additional potential significance to the concept of drug-mediated skin cancer nitrosogenesis [12-15].

Herein, we present another patient who developed keratoacanthoma and multiple actinic keratoses while taking telmisartan and tamsulosin. Based upon 1) the data available in the literature on nitroso contamination of both drugs (tamsulosin/telmisartan) [5] and 2) the additional data linking their intake to the development of keratinocytic and melanocytic tumors [9,10,16], we propose that drug-mediated photo-carcinogenesis is an essential element of skin cancer pathogenesis.

Case report.

An 88-year-old male came to the dermatology department with complaints of two tumor growths in the head region. The first, located on the forehead, developed over the previous six years following trauma from a car incident (Figure 1). He reported that the mass began to gradually enlarge months after the initial incident. A second lesion, located on the non-hairy part of the scalp, was first noticed about a month prior to presentation (Figure 2). The patient observed relatively rapid growth compared to the initial lesion.

The patient's medical history included arterial hypertension, benign prostatic hypertrophy, and surgery for a femoral head fracture performed three years previously. He reported being on antihypertensive therapy for approximately 20 years, with telmisartan 80 mg prescribed as one tablet in the morning and half a tablet in the evening for the past 5-6 years. Additionally, he had been taking tamsulosin hydrochloride 0.4 mg once daily in the evening for the past 7-8 years. No family history of skin cancer was reported.

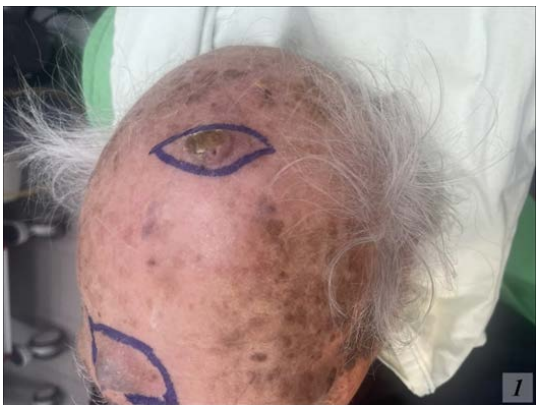

Figure 1. *Solitary, round nodular tumor on the vertex of the scalp with a centrally located hyperkeratotic zone extending beyond the lesion's border and altering the shape at that point. On the contralateral side, a separate nodular growth with a regular shape, defined borders, and a pink, raised, pearly edge is noted. The surrounding skin is severely sun damaged.*

Dermatological examination showed a solitary, round nodular tumor on the vertex of the scalp, with a centrally located hyperkeratotic zone extending beyond the lesion's border and altering the shape at that point (Figure 2). On the contralateral side, a separate nodular growth with a regular shape, defined borders, and a pink, raised, pearly edge was noted. Additionally, in the forehead region, a solitary, rounded nodular lesion measuring approximately 1.8 cm in diameter was identified (Figure 1). This formation had a flat, smooth surface, beneath which a centrally translucent blue-gray zone was visible, contrasting with the periphery, which matched the color of the surrounding skin. The surrounding skin was noted to be severely sun-damaged. Enlarged lymph nodes were not palpable.

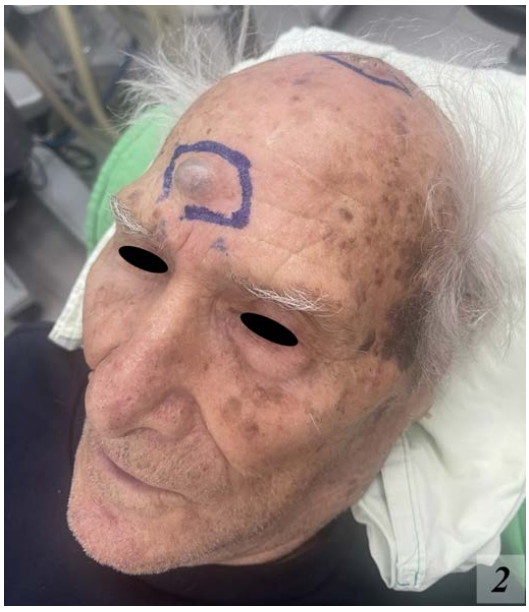

Figure 2. *A solitary rounded nodular lesion measuring approximately 1.8 cm in diameter in the forehead region. This formation exhibits a flat, smooth surface, beneath which a centrally translucent blue-gray zone is visible, contrasting with the periphery, which matches the color of the surrounding skin. The surrounding skin is severely sun damaged.*

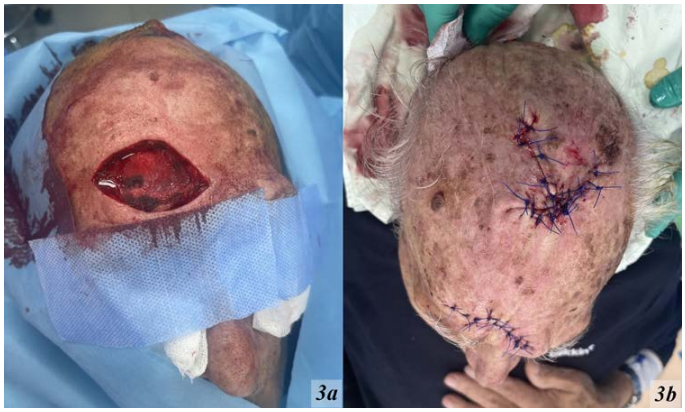

Figure 3a,b. *Intraoperative view.*
3a: *An elliptical excision of a tumor on the forehead resulted in a primary wound defect, with the marked lesion on the [capillitium] visible in the background.*
3b: *The wound defects on both the [capillitium] (upper lesion) and the forehead (lower lesion) were closed using single interrupted sutures.*

Under local anesthesia with 1% lidocaine, an elliptical excision was used to remove the lesion on the capillitium (Figure 3b). The primary wound defect was reconstructed with a modified advancement flap (Figure 3b), and the defect was closed with single interrupted sutures.

The lesion on the forehead was similarly excised with an elliptical excision (Figure 3a), and the resulting defect was managed using peripheral undermining of the wound edges to facilitate mobilization and primary closure of the wound edges.

The histopathological examination confirmed the lesion on the capillitium as keratoacanthoma and the forehead lesion as an epidermal cyst. For postoperative pain management, metamizole sodium one ampoule was prescribed, along with daily wound dressings with povidone-iodine.

The patient's therapeutic regimen was adjusted to telmisartan 80 mg once daily in the morning and tamsulosin hydrochloride 0.4 mg once daily in the evening.

Discussion.

The toxicokinetics of nitrosamines remain a mystery [17-19], though photochemical decomposition of nitrosamines is a known phenomenon [18]. It is unclear if nitrosamines exert their genotoxic effects locally after deposition in the skin and subsequent photodecomposition. The correlation between the formal administration of nitrosamines and their presence (or that of their products) in lesional tissue should be a solvable task for scientific teams. Moreover, it might minimize the need to conduct prospective followups, which have recently been losing their relevance!

Of interest are even more recent data concerning bacteria of the gut microbiome that are actively involved in the processing, activation, or conversion of some nitrosamines [17,19]. The activated nitrosamines in question are then able to exert their carcinogenic effects in a peripheral organ far from the zone of activation [17,19].

In experimental studies in rodents, it has been found that the bacteria encountered in the intestinal flora are found in even greater numbers in the skin [17,19]. The carcinogenic biotransformation of nitrosamines is apparently bacteria-dependent both in the gut and in the skin [17,19]. This proposed linkage to the skin microbiome may promote better understanding of the pathogenesis of Nitrosogenesis-induced skin cancer. For example, it remains an open question whether bacteria in the skin metabolize the nitrosamines identified in creams or cosmetic preparations to active carcinogenic metabolites with subsequent local genotoxic effects.

According to the most recent literature, the development of keratoacanthoma is also associated with direct exposure to ultraviolet light, fair skin type, and alcohol and tobacco consumption [20]. The latter two of these can also be regarded as ″nitrosamine-rich products″. Nitrosamines in tobacco are carcinogenic and mutagenic to humans, inducing mutations in the RAS oncogenes and p53 genes [21]. The question remains: are not nitrosamines in drugs also inducers of mutations in the development of skin cancer?

The same genes affected by nitrosamines are also key target genes affected in patients with keratinocytic tumors and melanoma [22-24]. This overlap of mutation patterns is unlikely to be coincidental, yet detailed analyses in the medical literature on this subject are lacking. According to some authors, nitrosamines are mediators between solar radiation and the occurrence of the mutations responsible for skin cancer [7,8,12,16].

There have been dynamic discussions on the `leading role' of UV radiation in the development of BRAF mutations [25-27]. Data on the potential role of another important mediator (genotoxin/phototoxin/mutagen), e.g. drug, in the face of so-called nitrosamines are still lacking or scarce [7-10,12-16]. Recently, multiple correlations have been established between the intake of nitrosamine-contaminated drugs and the subsequent generation of skin cancers; in particular, keratinocytic and melanocytic [11,14,28-31]. However, a limited number of

papers actually comment on the role of nitrosamines as an important etiological factor in these observations [7-10,12-16,32-35].

The question remains: is there no cumulative nitrosamine toxicity, when it is known that: 1) nitrosamines are activated in the skin via the skin microbiome , during topical application of preparations, or after contact with aerosolized, nitrosamine-rich particles falling on the skin; 2) there is direct phototoxic action of nitrosamines upon the skin, after application of topical preparations in the form of contaminated creams, and a direct phototoxic action of their active metabolites generated in the body after metabolism by intestinal flora and in the liver and subsequent deposition in the skin; and 3) there is direct carcinogenic action after deposition in the skin and subsequent phototoxicity? Are nitrosamine products mutagenic following photodecomposition?

The questions regarding patient safety and the mechanisms of nitrosamines in skin exposed to solar radiation remain especially relevant but also - at the moment - unsolved [25,26].

Regulatory tests do not fully capture the complexity of issues concerning the genotoxicity and phototoxicity of nitrosamines and their impact on humans. Their various forms of metabolism and activation, and their somewhat obscure toxicokinetics, are also likely reasons why the carcinogenicity tests of regulators begin to fail even before they are fully established [6].

The processes of carcinogenesis and metabolic reprogramming of the tumor cell are complex and multifactorial [7,32-33]. They cannot be characterized through data from static tests such as the Ames test, or even the so-called CPCA test. These facts have been repeatedly acknowledged on a scientific level, at numerous congresses and conferences [36,37].

Dynamic conditions and observations through clinical practice remain the cornerstone of basic science. When these observations are neglected and the focus shifts elsewhere, the result is apparent: in this particular case, a drastic jump in the incidence of skin cancer worldwide, continued exposure to carcinogen-contaminated drugs worldwide, and poly-medication without borders. Elimination regimes for carcinogens/mutagens in pharmaceuticals, also known as nitrosamines, should become a priority.

REFERENCES

1. Nishie K, Norred WP, Wasserman A, et al. Phototoxicity and differential hepatotoxicity as biological indicators of nitrosamine activity. Toxicol Appl Pharmacol. 1972;23:680-691.
2. 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.
3. Schmidtsdorff S, Neumann J, Schmidt AH, et al. Prevalence of nitrosamine contaminants in drug samples: Has the crisis been overcome? Arch Pharm (Weinheim). 2023;356:e2200484.
4. White CM. Ranitidine's N-nitrosodimethylamine Problem May be Tip of the Iceberg. JAMA Netw Open. 2021;4:e2035158.
5. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cder-nitrosamine-impurity-acceptable-intake-limits
6. Thomas DN, Wills JW, Burman M, et al. Resolution of Historically Discordant Ames Test Negative / Rodent Carcinogenicity Positive N-nitrosamines using a Sensitive, OECD-aligned Design. Mutagenesis. 2024:geae027.
7. Tchernev G, Ivanov L. MUSTARDE ROTATION FLAP AS ADEQUATE OPTION FOR HIGH-RISK BCC NEAR THE LOWER EYE LID: THE ADDITIONAL INTAKE OF N-NITROSO-FOLIC-ACID AND N-NITROSO-RIVOROXABAN AS COFACTORS/TRIGGERS OF THE METABOLIC REPROGRAMMING OF THE FUTURE CANCER CELL. Georgian Med News. 2024;351:131-137.
8. Tchernev G, Broshtilova V, Kordeva S. SHARK PEDICLE ISLAND FLAP FOR BASAL CELL CARCINOMA OF THE PERIALAR ZONE OF THE NOSE: PHOTOXICITY AND PHOTOCARCINOGENICITY MEDIATED BY POTENTIALLY NITROSAMINE CONTAMINATED DRUG INTAKE -A NEW EXPLANATION FOR THE SKIN CANCERS PATHOGENESIS? Georgian Med News. 2024;352-353:218-222.
9. Tchernev G, Bitolska A, Patterson JW. Telmisartan (and/or nitrosamine) - induced occult melanoma: first reported case in world literature. Expert Rev Clin Pharmacol. 2021;14:1075-1080.
10. Tchernev G, Patterson JW. Telmisartan/hydrochlorothiazide-induced nevus-associated cutaneous melanoma: first report in the medical literature. Expert Rev Clin Pharmacol. 2021;14:289-293.
11. Kuntz T, Grimm A, Hofmann SC, et al. Hydrochlorothiazide and increased risk of atypical fibroxanthoma and pleomorphic dermal sarcoma. J Dtsch Dermatol Ges. 2024;22:513-519.
12. Tchernev G, Dimova D. 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. Georgian Med News. 2024;347:136-141.
13. Tchernev G, Dimova D. PERIOCULAR HIGH RISK BCCS AFTER ADDITIONAL/PARALLEL INTAKE OF TORASEMIDE, MOXONIDINE AND MIRABEGRON: IMPORTANT LINKS TO SKIN CANCER RELATED (PHOTO-) NITROSOGENESIS IN THE CONTEXT OF PHARMACO-ONCOGENESIS. Georgian Med News. 2024;347:70-76.
14. Tchernev G, Naydekova N. MELANOMA AND DYSPLASTIC NEVI DEVELOPMENT AFTER RANITIDINE/ RILMENIDINE/MOXONIDINE, LERCANIDIPINE, ROSUVASTATIN AND VERAPAMIL/TRANDOLAPRIL - NEW DATA/CASE SERIES. THE POTENTIAL ROLE OF NITROSAMINE/NDSRIS CONTAMINATION IN POLYMEDICATION AS SUBSTANTIAL SKIN CANCER TRIGGERING FACTOR. Georgian Med News. 2023;344:152-158.
15. Tchernev G. THE NITROSAMINE CONTAMINATION IN BETA BLOCKERS (BISOPROLOL/METOPROLOL), ACE INHIBITORS (LISINOPRIL/PERINDOPRIL),

THIAZIDES DIURETICS (HCT), CALCIUM CHANNEL BLOCKERS (AMLODIPINE/FELODIPINE), SARTANS (CANDESARTAN) AND THE SUBSEQUENT SKIN CANCER DEVELOPMENT AND PROGRESSION: APOCALYPSE NOW. Georgian Med News. 2023;337:138-145.
16. Tchernev G, Todorov I, Ivanov L, et al. Basal cell carcinoma development after combined administration of Lisinopril and tamsulosin: Links to Photocarcinogenesis and Nitrosogenesis in the context of Pharmaco-oncogenesis. J Medical review (Bulgarian). 2024;60:67-72.
17. https://www.genengnews.com/topics/omics/gut-microbiome-links-carcinogen-metabolism-to-tumor-formation/
18. Magee PN. Toxicity of nitrosamines: their possible human health hazards. Food Cosmet Toxicol. 1971;9:207-218.
19. Roje B, Zhang B, Mastrorilli E, et al. Gut microbiota carcinogen metabolism causes distal tissue tumours. Nature. 2024;632:1137-1144.
20. Claeson M, Pandeya N, Dusingize JC, et al. Assessment of Incidence Rate and Risk Factors for Keratoacanthoma Among Residents of Queensland, Australia. JAMA Dermatol. 2020;156:1324-1332.
21. 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.
22. Boeckmann L, Martens MC, Emmert S. Molecular Biology of Basal and Squamous Cell Carcinomas. Adv Exp Med Biol. 2020;1268:171-191.
23. Sung WW, Chang CH. Nevi, dysplastic nevi, and melanoma: Molecular and immune mechanisms involving the progression. Tzu Chi Med J. 2021;34:1-7.
24. Campos MA, Macedo S, Fernandes MS, et al. Prognostic Significance of RAS Mutations and P53 Expression in Cutaneous Squamous Cell Carcinomas. Genes (Basel). 2020;11:751.
25. Besaratinia A, Pfeifer GP. Sunlight ultraviolet irradiation and BRAF V600 mutagenesis in human melanoma. Hum Mutat. 2008;29:983-91.
26. Viros A, Sanchez-Laorden B, Pedersen M, et al. Ultraviolet radiation accelerates BRAF-driven melanomagenesis by targeting TP53. Nature. 2014;511:478-482.
27. Laughery MF, Brown AJ, Bohm KA, et al. Atypical UV Photoproducts Induce Non-canonical Mutation Classes Associated with Driver Mutations in Melanoma. Cell Rep. 2020;33:108401.
28. Hou A, Li Y, Shadyab AH, et al. Photosensitizing antihypertensive medication and risk of skin cancer among postmenopausal women. J Dtsch Dermatol Ges. 2024;22:186-194.
29. Tchernev G. NITROSOGENESIS OF CUTANEOUS MELANOMA: SIMULTANEOUSLY DEVELOPMENT OF PRIMARY CUTANEOUS THICK MELANOMA OF THE BREAST, THIN MELANOMA/DYSPLASTIC MOLE OF THE BACK DURING PARALLEL INTAKE OF BISOPROLOL, AMLODIPINE AND VALSARTAN/ HCT: NITROSAMINE POLYCONTAMINATION IN THE MULTIMEDICATION AS THE MOST POWERFUL SKIN CANCER TRIGGER. Georgian Med News. 2023;339:83-88.
30. Hashizume H, Nakatani E, Sasaki H, et al. Hydrochlorothiazide increases risk of nonmelanoma skin cancer in an elderly Japanese cohort with hypertension: The Shizuoka study. JAAD Int. 2023;12:49-57.
31. 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.
32. Tchernev G, Ivanov L, Broshtilova V. MULTIPLE KERATINOCYTIC CANCERS AFTER INTAKE OF ANTIHYPERTENSIVES (LISINOPRIL/BISOPROLOL/ HCT) AND ANTIARRHYTMICS (PROPAFENONE): THE IMPORTANT NEW LINKS TO THE NITROSO-CONTAMINATION AND THE METABOLIC REPROGRAMMING OF THE FUTURE CANCER CELL. Georgian Med News. 2024;351:65-71.
33. Tchernev G, Broshtilova V. (NDMA) METFORMIN AND (NTTP) SITAGLIPTIN INDUCED CUTANEOUS MELANOMAS: LINKS TO NITROSOGENESIS, NITROSO-PHOTOCARCINOGENESIS, ONCOPHARMACOGENESIS AND THE METABOLIC REPROGRAMMING. Georgian Med News. 2024;348:132-143.
34. Tchernev G. METASTATIC NODULAR MELANOMA DEVELOPING ON NEVUS SPILUS DURING INTAKE OF BETA BLOCKERS (BISOPROLOL/NEBIVOLOL) AND ACE INHIBITORS (PERINDOPRIL). POTENTIAL LINKS TO THE DRUG RELATED NITROSOGENESIS/ CARCINOGENESIS, DUNNING-KRUGER EFFECT AND GENETIC WEAPONS OF THE NEW GENERATION. Georgian Med News. 2023;343:172-178.
35. Tchernev G, Lozev I, Ivanov L. MORPHEAFORM BCC OF ALA NASI: A SUCCESSFUL DERMATOSURGICAL APPROACH BY TRANSPOSITION FLAP FROM THE ADJACENT AREA. CONTAMINATION OF VENLAFAXINE, BISOPROLOL AND OLANZAPINE WITH NITROSAMINES/NDSRIS: THE MOST LIKELY CAUSE OF SKIN CANCER DEVELOPMENT AND PROGRESSION. Georgian Med News. 2023;342:26-29.
36. Tchernev G, Oliveira N, Kandathil LJ, et al. 4th National Congress of the Bulgarian Society for Dermatologic Surgery, Sofia, 12th March 2022 with main topics: one step melanoma surgery and drug induced melanoma. Dermatol Reports. 2022;14:9542.
37. 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;337:89-95.
38. Lewis D, Mama J, Hawkes J. A Review of Aspects of Oxidative Hair Dye Chemistry with Special Reference to N-Nitrosamine Formation. Materials (Basel). 2013;6:517-534.
39. Schettino L, Benedé JL, Chisvert A. Determination of nine prohibited N-nitrosamines in cosmetic products by vortex-assisted dispersive liquid-liquid microextraction prior to gas chromatography-mass spectrometry. RSC Adv. 2023;13:2963-2971.