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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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NITROSOGENESIS LESSONS FROM DERMATOLOGISTS-NITROSAMINES/ NDSRIS CONTAMINATION OF THE POLIMEDICATION IN POLIMORBID PATIENTS AS THE MOST POWERFUL SKIN CANCER INDUCTOR: DOUBLE HATCHET FLAP FOR SCC OF THE SCALP OCCURRING DURING TREATMENT WITH VALSARTAN/ HYDROCHLOROTHIAZIDE AND LERCANIDIPINE

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Abstract.

Nitrosogenesis remains to be a topic that is and, in all likelihood, will be relevant in the near and distant future. The reason for this actuality is mainly due to the official data of the regulatory authorities in the face of the FDA, starting back in 2018 with the announcement of the contamination of Valsartan with nitrosamines. This issue only became more profound in April 2023, when again the FDA declared over 250 of the most widely distributed drugs worldwide as actually or potentially contaminated with ″hypothetical″ carcinogens. Unfortunately, according to the literature, it is the intake of ″hypothetical carcinogens″ that is associated with the development of real carcinomas, including cutaneous tumours. Additionally, the type of carcinogens that could ″hypothetically″ be found in these drugs (in the regulatory agency recommendations) has been added to the list, and they are categorized as having a ″hypothetical carcinogenic potency″ between 1 to 5 according to the FDA regulation as to pharmaceutical companies from August 2023.

Reference values have also been established for each carcinogen.

Interestingly , in certain geographic regions such as Eastern Europe, for example, in certain institutions, over periods of 10 years or more, over 98.9% of cases of actual cutaneous tumours (keratinocytic, melanocytic, etc.), could be linked/ associated primarily (not hypothetically) to polymedication, which according to official FDA data from April 2023, could be defined as actually/potentially contaminated with up to several ″hypothetical″ carcinogens simultaneously. The lack of official data on the contamination of these batches of drugs (with nitrosamines/ NDSRIs) remain even for the period 2018-2023 more than worrying and are one indirect evidence of their real rather than hypothetical availability.

Nonetheless, the 2023 FDA data cast considerable doubt as to whether, within the polymorbidity and contamination of polymedication, the allowable daily doses of carcinogens are being substantially exceeded. An open question for regulators remains: Did the giant Pfizer withdraw its high blood pressure drugs in 2022 (hydrochlorothiazide, quinapril) due to the presence of ″hypothetical carcinogens″?

In practice, Pfizer appears to be one of the few or only companies to have openly stated the reason for withdrawing their preparations due to contamination with real carcinogens and thus protect end users. With this official preventive act, the Giant Pfizer gained the trust of patients worldwide.

Another and even more serious dilemma remains whether this is a controlled contamination of certain batches of medicines in certain geographical regions? Indicative therefore are recently published data on the absence of contamination of all batches of a certain class of medicines in certain geographical regions. The genesis of the 'sporadicity' and the 'selectivity' of contamination remain for the time being unresolved and open new and novel questions.

We present an 82-year-old patient with arterial hypertension taking hydrochlorothiazide, valsartan and lercanidipine for 3 years who developed a short-term squamous cell carcinoma of the scalp after taking them (1,5- 2 years later) , operated successfully by double hatchet flap. The pathogenesis of the skin tumor/keratinocytic cancer is commented in the context of nitrosogenesis and the officially announced contamination by the FDA with ″hypothetical carcinogens″ leading once again to the appearance of a real squamous cell carcinoma of the skin. The polycontamination of multimedication within polymorbidity appears to be problematic. It is thanks to the official FDA data that the strength of these interrelationships is beginning to become clearer although not at the desired speed of clinicians and end users.

Discovering the logical relationship between databases (concerning the incidence of skin cancer, but not only) from different periods should only be relative or consistent with current bulletins of regulators and contaminated polymedication. This is what guarantees that the objective truth will be brought to the surface and ensure, through the possible rapid elimination of the contaminants: 1) better survival for patients and 2) better quality of life.

Key words. Nitrosogenesis, keratinocyte cancer, NDSRIs, Nitrosamines, lercanidipin, hydrochlorothiazide, policontamination, FDA, double hatchet flap.

Introduction.

The issue of epithelial skin tumors/ keratinocytic skin cancer and the use of various drugs has been a current issue for years , often involving the drug hydrochlorothiazide [1-7].

Recent data in one of the most peer-reviewed dermatological journals highlight a significant association between the high cumulative hydrochlorothiazide use (≥ 5,000 defined daily dose; ≥ 125,000 mg) and the risk of any skin cancer (adjusted hazard ratio 5.32, 95% confidence interval (95% CI) 2.40-11.81), keratinocyte carcinoma (adjusted hazard ratio 7.31, 95% CI 3.12-17.13), basal cell carcinoma (adjusted hazard ratio 7.72, 95% CI 3.11-19.16) and squamous cell carcinoma (adjusted hazard ratio 19.63, 95% CI 3.12-123.56) [8].

The occurrence of this type of tumors (keratinocytic cancer) according to other authors' collectives, is due to the occurrence of photosensitivity after the intake of thiazide diuretics, in

addition to the presence of certain carcinogens, also known as NDSRIs/ nitrosamines [9,10].

It is also only this sporadic, probably somewhat (according to some authors) and ″controlled (?) contamination″ of hydrochlorothiazide (but not only) that could explain the divergent results of a number of international studies [11]. These contradictory results are also a cause of confusion as well as a certain amount of confusion/uncertainty in the academic community.

There are other data in the world literature that describe nitrosamines as a key factor in the development of keratinocytic cancer after/within the combined intake of potentially/really contaminated sartans (olmesartan/valsartan) in combination with hydrochlorothiazide [9].

The situation is analogous within multimedication, and intake of calcium antagonists (amlodipine/ felodipine) contaminated with nitrosamines and the development of keratinocytic cancers [10].

The patient described within this publication presents with the development of a very likely drug-induced spinocellular carcinoma of the scalp within the context of actual/potential nitrosamine-contaminated antihypertensive drugs: valsartan, hydrochlorothiazide, and lercandipine.

The dose-dependent time intervals required for tumour initiation, and the pattern of equivalent clinical patterns (either of skin cancer manifestation or its precursor forms after intake of nitrosamine/NDSRIs contaminated with different classes of drugs), could be considered as at least indicative of such a relationship.

Case report.

We report an 82-year-old patient attending the outpatient clinic of dermatology and dermatologic surgery for a new-onset tumor-like lesion of approximately 1-1.5 years' duration localized in the scalp area (Figure 1) . A year ago, he underwent outpatient cryotherapy of the scalp due to suspected actinic keratoses without histopathological verification of the latter. The co-morbidities were known to be varicose veins of the lower limbs and arterial hypertension with a history of 10 years. Systemic medication at the time of presentation to the outpatient clinic included 1) valsartan 160/hydrochlorothiazide once daily from January 2020 to 09/ 2023; 2) lercanidipine 10 mg once daily for 3 years. According to history, the patient was taking other medications for his hypertension, but these could not be clarified at the time of hospitalization.

Within the dermatological examination in the area of the capillitium, parietally on the right, a single ulcer-nodular lesion of irregular shape and size of 7.5 by 4.5 cm, covered with yellowish exudate, in places peripherally forming dense brownish crusts, as well as a confluent dorsomedially localized satellite erosive lesion covered with a tightly adherent crust (Figures 1 and 2). Clinically and dermatoscopically, the lesion was suggestive of a keratinocytic skin tumor. Paraclinical and apparative diagnostic procedures were without evidence of metastasis. Surgical removal under local anesthesia was planned with moderate cardiogenic risk and the need for close monitoring during the intervention. After disinfection of the surgical site and placement of local anesthesia with lidocaine

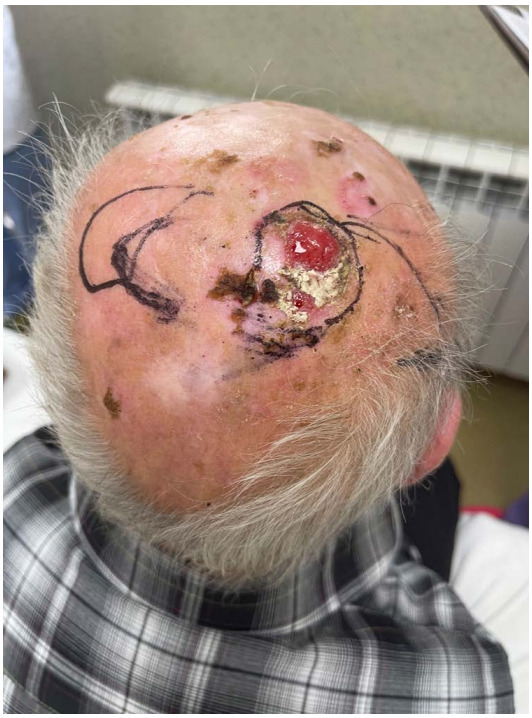

Figure 1. *Epithelial tumour (SCC) formation in the occipito parietal scalp region.*

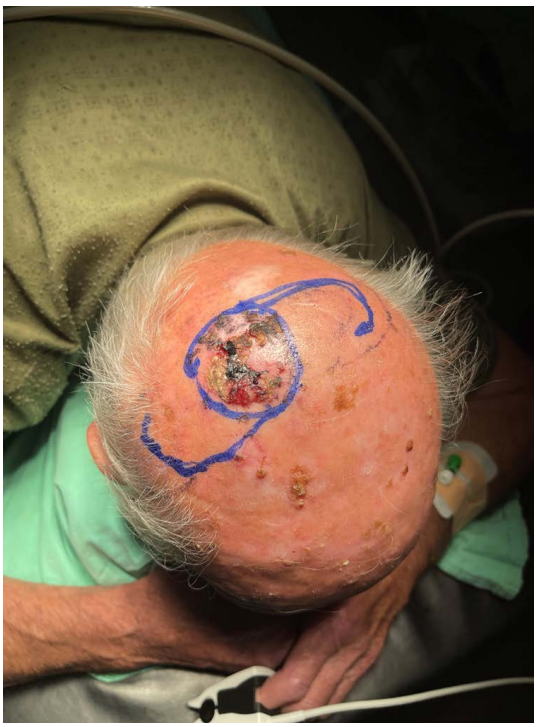

Figure 2. *Preoperative marking of resection fields.*

1%, oval excision of the primary tumor was performed with a surgical margin of safety of 0.5 cm in all directions (Figure 3), followed by a double hatchet flap with rotation and adaptation of the wound edges in the periphery (Figures 4-7). Subsequent histopathological verification was indicative of G2 squamous cell carcinoma of the skin, with infiltration of one resection line. The staging was determined to be T2N0M0R1. Clinical observation of the patient and re-excision if necessary was recommended.

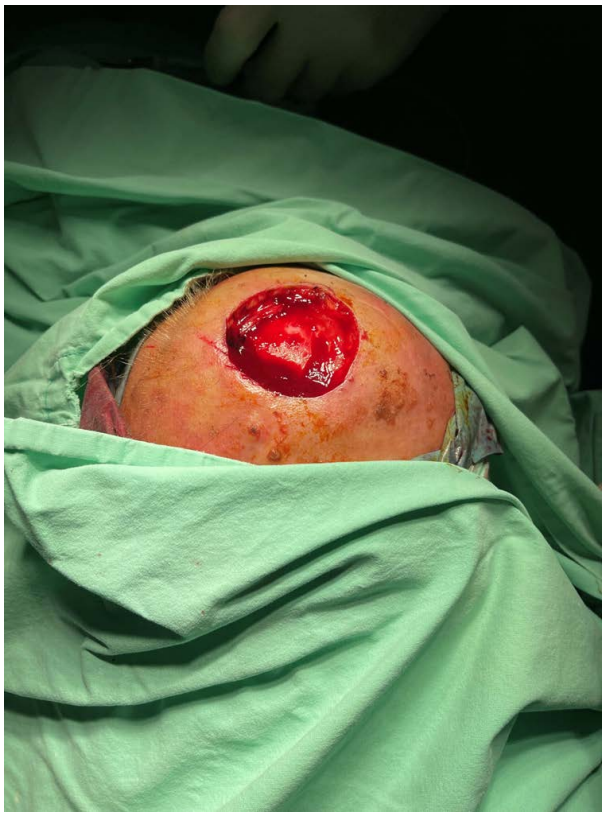

Figure 3. *Oval excision of the tumor.*

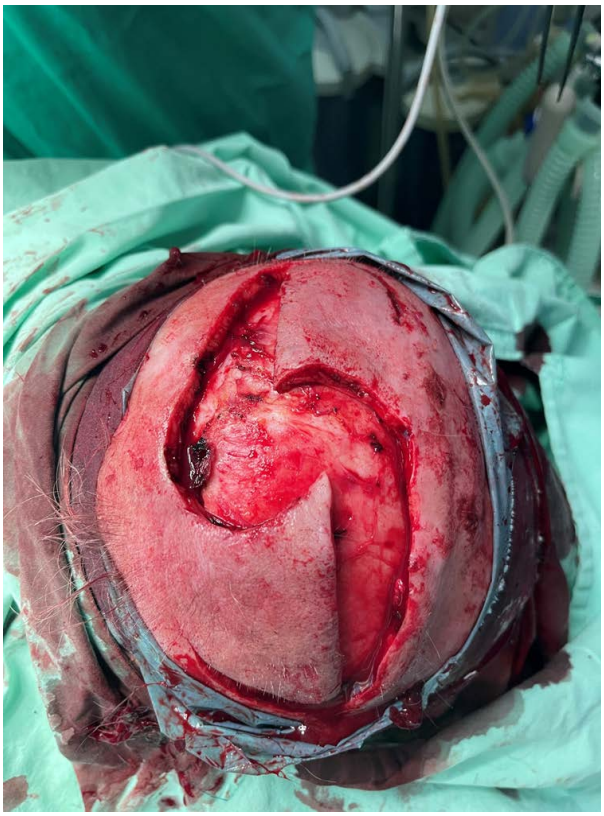

Figure 5. *Formation of a Z-shaped defect.*

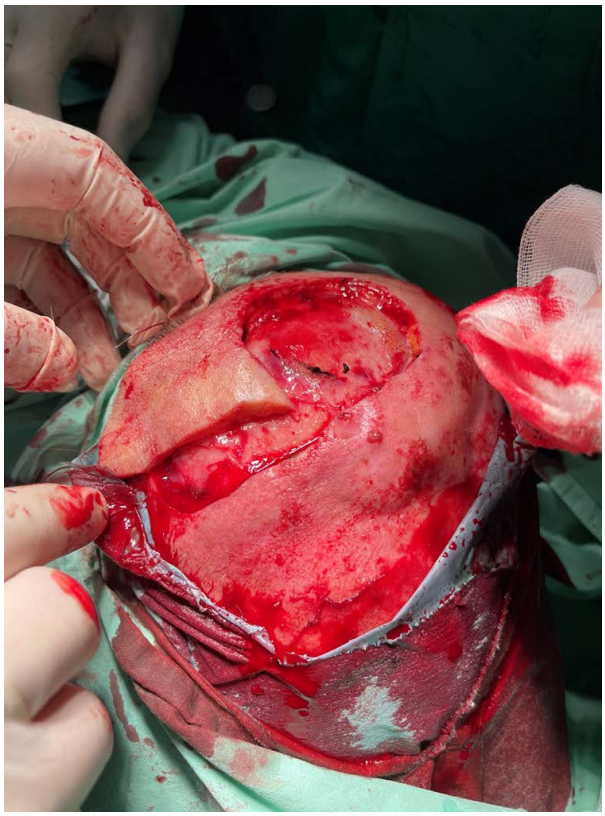

Figure 4. *Staged skin preparation after tumor removal.*

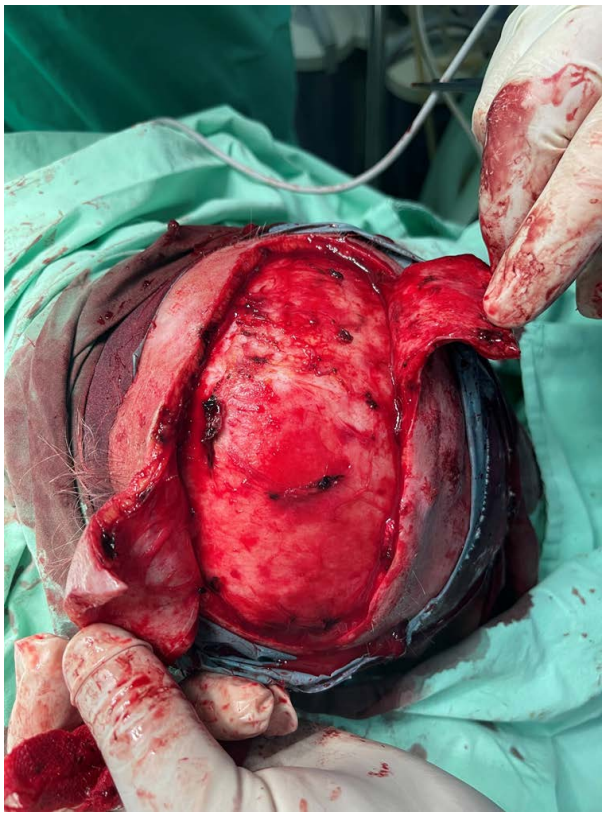

Figure 6. *Visualization of the defect after lifting both flaps and stopping the bleeding.*

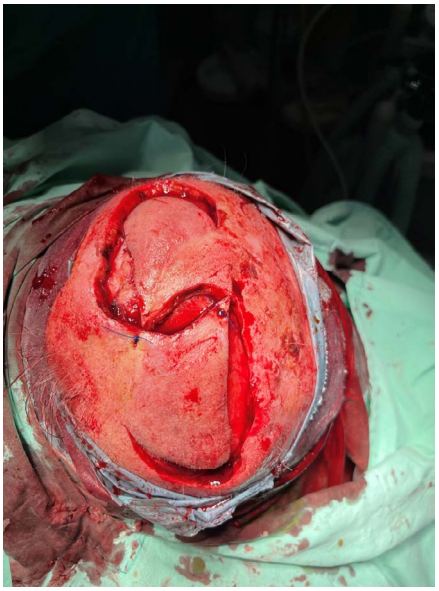

Figure 7. *Fixation of flap edges with situational sutures before starting staged wound edge adaptation.*

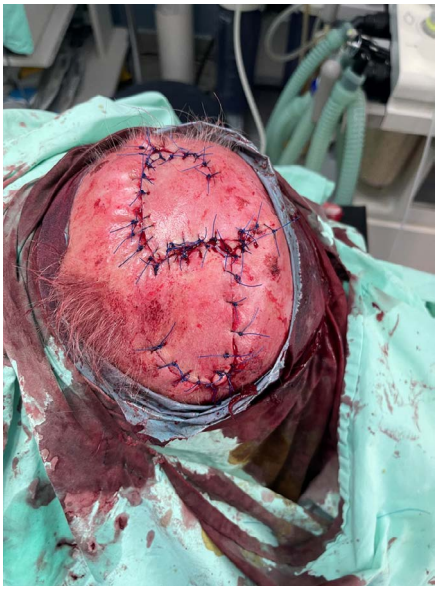

Figure 8. *Clinical findings immediately after surgery and closure of the defect.*

Figure 9. *Clinical picture on postoperative day 18.*

Discussion.

Contamination of polymedication in polymorbid patients is a reality that has been formally initialized as a recommendation by control authorities/FDAs to manufacturers and currently includes over 250 drugs as actually/potentially contaminated with nitrosamines/FDAs, April 2023 [12]. Possible contaminants in each drug are classified by class on the basis of their carcinogenic potency and the reference contaminant levels for each carcinogen, NDSRIs are indicated [12,13].

Both of these regulatory recommendations do not take into account the concomitant/parallel intake of polycontaminated drugs, which could lead to the development of single or multiple skin cancers, as described repeatedly in the medical literature [9,10,14], as shown in the patient presented by us in this paper.

In practice, the FDA recognizes (1) the presence of potent ″hypothetical carcinogens″ in drugs taken by more than 5 billion patients worldwide [12]; (2) defines 5 subcategories of their ″hypothetical carcinogenic potency″ [13], and (3) reference values for permissible, tolerable intakes of these ″hypothetical carcinogens″ for more than 250 drugs [13].

What this means in practice: 1) carcinogens in drugs are present. Otherwise, their availability would not have been indicated as an official FDA document in April 2023 [12]; 2) within the mono- and/or poly-medication they cannot be avoided/ could hardly be avoided and this has consequences [9,10,14] as in the patient presented in this scientific work; 3) the permissible doses per day within polycontamination could safely be exceeded many times (difficult to ascertain due to lack of official data from checks for nitrosamines in relevant batches/ confidentiality of check results worldwide), [9,10,14]; 4) Multi-medication in polymorbid patients could in this very way cause heterogeneous cancers, including keratinocytic cancers [9,10,14]. And: 5) for accurate reference limits to be set for ″hypothetical carcinogens″, it is more than obvious that data are available indicating , that drug intake outside these limits could be problematic for patients: or ″hypothetical carcinogens″ become real. But for the moment, even these regulatory data remain hidden from the academic community.

Sartans have been described by the FDA as potentially contaminated with some of the most severe carcinogens/ NDSRIs, possessing carcinogenic potency analogous to the already well known NDMA, NDEA and NMBA [15].

The contamination of hydrochlorothiazide with nitrosamines was officially announced by Pfizer in 2022 and batches of this drug were officially withdrawn from the market [16].

Strange why, though- both valsartan and hydrochlorothiazide do not appear on the most recent official FDA list of 08.04.2023, defining acceptable daily intake levels of ″hypothetical carcinogens″ in preparations worldwide [12].

Lercanidipine taken by the patient is also not included in the list of potentially/actually nitrosamine-contaminated/ NDSRIs/ drugs , which however does not exclude its later accreditation/ inclusion in a possible future update of this list.

The polycontamination of multimedication and keratinocyte cancer generation within the so-called cutaneous nitrosogenesis is the most advanced and current concept concerning carcinogenesis and skin cancer in general [9,10,14]. Its

detailed study and elucidation would lead to a drastic decline in skin cancer incidence worldwide [9,10,14]. Estimates of the incidence of keratinocytic cancer in general remain alarming and are increasing with each passing year [17]. A potential link could be sought between this incidence and the formally paraphrased intake of `hypothetical carcinogens' by regulators, leading in the short term to real skin cancers [9,10,14].

The presence of these carcinogens/nitrosamines/NDSRIs within a combined intake (of sartans/ valsartan with hydrochlorothiazide and/or with calcium antagonists) has been documented repeatedly in the medical literature as a possible trigger for keratinocytic cancer [18-21].

Keratinocytic form of cancer (basal cell carcinoma) has been previously described after combined administration of lercanidipine in combination with valsartan and hydrochlorothiazide, potentially/actually contaminated with nitrosamines [22].

Large-scale retrospective analyses by other colleagues have associated monomedication with sartans, as well as that with hydrochlorothiazide, with the development of squamous cell carcinomas of the skin [23]:

Monomedication with sartans was associated with a relatively high risk of developing squamous cell carcinomas: Unadjusted OR (95% CI): 2.50 (1.93- 3.23)/Adjusted OR (95% CI): 2.22 (1.37- 3.61) [23]. The risk of developing squamous cell carcinomas after intake of sartans/ARBs was more than doubled and remained constant [23].

Monomedication with hydrochlorothiazide was indicative of an available serious risk of developing squamous cell carcinomas, which after stratification reached 4-fold higher : OR (95% CI): 2.97 (2.33- 3.79) / Adjusted OR (95% CI): 4.11 (2.66- 6.35) [23].

Combined intake of both drugs (hydrochlorothiazides valsartan) in all likelihood poses serious health risks to patients. Recent studies on the association of thiazide diuretics and the risk of keratinocytic skin cancer from 2023 in the Journal of the American Academy of Dermatology [2], strongly support the data of Nardone B et al. [23] on the available risk of developing keratinocytic tumors and melanoma after hydrochlorothiazide intake [24]. The objectivity of these follow-up studies could not be questioned, and the correct line of thinking regarding this possible pathogenetic link has been reestablished [23,24], strongly concordant with subsequent observations by colleagues, dermatologists from Eastern Europe [9,10,14].

The third drug taken by the patient is lercanidipine, for which nitrosamine contaminations are not new and are in fact possible [25] but are probably currently in the process of clarification of their carcinogenic potency/reference values and therefore probably not yet on the 2023 FDA list of potential carcinogens in drugs [12].

Reconstructive options to cover defects after surgical removal of tumors in the scalp area include the application of various flaps: from double hatchet flap [26], rotation advancement flap [27], triple rhombic flap [28], H-flap [28] and many others. The double hatchet flap performed in the scalp area in the described patient showed very good postoperative results, and the postoperative period passed without complications (Figures 8 and 9).

In addition to the fact that the scientific work represents a benchmark of a perfectly executed complex dermatosurgical technique (double hatchet flap), (Figures 3-7) with a subsequent perfect final result (Figures 8 and 9), it draws attention to a considerably more important fact: polycontamination with ″hypothetical carcinogens″/ NDSRIs, nitrosamines in the framework of multimedication in polymorbid patients, is able to short-term lead to the manifestation of single (or in other cases -multiple cutaneous tumors). This timeframe is of the order of 1-1.5 years and depends on the extent of contamination of each affected class of the three drugs being administered: valsartan, lercanidipine and hydrochlorothiazide. Unfortunately, the data on single contaminations of each class of drugs, including those mentioned above, remains confidential and there are good reasons behind this confidentiality. Reasons that are in all likelihood ″hypothetically worrisome″.

The unraveling of the concept of nitrosogenesis is currently at an advanced stage and the data on side effects could not remain concealed as in the last 40-50 years.

It is the duty of every clinician to make his or her own thorough analysis of the available data at the institution where they work, and the results should inevitably be made public for the benefit of the academic community and patients.

Unravelling the puzzle of carcinogenesis cannot become a reality unless the data concerning the nitrosogenesis of skin cancer, but also of cancer in general, are formalised. These data are available and in front of our eyes. The staggering rates of rising cancer incidence worldwide and their estimated rates over a 20-year period [29] are absolutely and unequivocally in accordance with the growing number of nitrosamines/NDSRIs in number and type, as well as the drugs affected by them (over 250 at present) [12].

Future statistical analysis of these data, with respect to polymedication in polymorbid patients, would conclusively prove the leading role of nitrosogenesis in generating keratinocytic cancers (but not only), at least as an unconditional cofactor.

Last but not least, a publication by a Turkish collective should be commented on and analysed, declaring the absence of any contamination of all sartans that have been screened for the presence of nitrosamines/NDSRIs in Turkey [30]. This effectively means that ″with good will″ on the part of the producers, contamination could be eliminated in the short term or more quickly than expected.

The dilemma remains: ″How to potentiate the billion-dollar heavy pharmaceutical companies to increasingly manifest this so deeply hidden goodness of theirs?″

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