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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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NITROSAMINES IN METFORMIN AND HYDROCHLOROTHIAZIDE: ″HUMAN SAFE PHOTOCARCINOGENS″ WITHIN THE POLYPHARMACY AS GENERATOR FOR PHOTOTOXICITY/ PHOTOCARCINOGENICITY AND THE SUBSEQUENT DEVELOPMENT OF MULTIPLE KERATINOCYTE CARCINOMAS. DOUBLE HATCHET FLAP AS OPTIMAL AND NECESSARY DERMATOSURGICAL DECISION IN TWO NEW PATIENTS

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Abstract.

The issues that have been identified to date as potentially pivotal in relation to skin cancer in general, but also keratinocytic cancer in particular, mainly concern the permanent potentiation of concepts such as phototoxicity and hence its subsequent photocarcinogenicity over time.

Studies by scientific teams dating back more than 50 years have defined the phototoxicity of nitrosamines as a rather non-specific property, regardless of whether the last mentioned have a carcinogenic effect or not.

Recently or in 11/ 2024, hydrochlorothiazide was officially declared by the IARC/ International agency on cancer research as carcinogenic to humans due to its phototoxicity. Similar to sartans, metformin, beta blockers and calcium antagonists, hydrochlorothiazide are also associated with contamination from nitrosamines and all of them are scientifically and pathogenetically linked to phototoxicity and carcinogenicity in humans.

The photocarcinogenic risk of those drugs in humans based on availability of nitrosamines in drugs seems to remain in all likelihood uncalculated by the regulators' tests, which are tailored to assess the purely carcinogenic risk, which in practice is also inaccurately calculated for a number of points.

The cumulative phototoxicity and subsequent photocarcinogenicity in humans differ from pure carcinogenicity in bacteria and rodents.

According to a number of international clinical observational studies, concomitant use of more than 1 antihypertensive drug is also associated with a significantly higher risk of developing skin cancer, and in patients with diabetes mellitus this risk is further increased.

Polymedication of potentially contaminated drug production is logically associated pathogenetically with the intake of a larger amount of photocarcinogens and/or mutagens in parallel.

The present article highlights and is indicative of the following facts: nitroso (photo)carcinogenesis is an undeniable fact that is integral to photocarcinogenesis and skin cancer pathogenesis.

Nitrosogenesis of skin cancer is mediated and regulated most likely by the nitrosamine content of drugs.

Drug-mediated Photo nitroso genesis/ Carcinogenesis of skin cancer accounts for the occurrence and progression of a significantly greater number of tumors compared to pure Photocarcinogenesis.

Permanent intake of potentially contaminated polymedication leads to clinical manifestation of multiple skin tumors.

We present two cases of patients who developed scalp tumors treated successfully with double hatchet flap. One of them developed a scalp tumor but also an additional auricular tumor in the context of a potential nitrosamine-contaminated polydrug regimen including 1) metformin, 2) bisoprolol, 3) amlodipine/ valsartan/hydrochlorothiazide. The double hatchet flap technique and the role of drug-induced Nitroso Carcinogenesis/ Photo Nitroso Carcinogenesis/Oncopharmacogenesis due to the permanent intake of phototoxic, genotoxic substances (within drugs), also known as nitrosamines, is commented. Complete elimination regimens of nitrosamines in drugs appear to be the safest solution to this global problem concerning skin cancer and cancer in general worldwide.

Key words. Epithelial skin cancer, scalp basal cell carcinoma, double hatchet flap, metformin, bisoprolol, amlodipine/ valsartan/ hydrochlorothiazide, phototoxicity, nitrosogenesis, oncopharmacogenesis, Photo Nitroso Carcinogenesis, NDMA.

Introduction.

Over the years, it has been well established that skin cancer development is primarily linked to solar ultraviolet radiation (UV), which is recognized as a major causative factor [1]. Excessive or cumulative sun exposure is associated with both melanocytic and nonmelanocytic skin cancers, which are often manifesting years or even decades after exposure [1]. The absorption of ultraviolet radiation leads to DNA damage in epithelial cells [2], with UV-induced DNA photoproducts capable of triggering specific mutations in genes susceptible to squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) [1].

Mutations in genes related to the Hedgehog signaling pathway, particularly PTCH1, have been identified as key contributors to BCC development [1]. Despite the strong pathogenetic link between basal cell carcinoma and cumulative UVB radiation,

specific UV-induced mutations are detected in only half of sporadic BCC cases [1]. Therefore, while UV exposure is a significant etiological risk factor/carcinogen [3], it cannot be considered the sole contributor for BCC development [1].

The most common locations for basal cell carcinoma development are the head and neck regions, which are among the most chronically sun-exposed areas of the skin [4]. Although BCC is generally considered a less aggressive skin cancer, it can be locally invasive and may lead to significant complications and morbidity in patients [5]. However, complete surgical excision with clean resection margins remains the gold standard, particularly for lesions in challenging anatomical areas such as the head and neck [5]. In these regions, primary wound defects can sometimes be too large to close with simple suture techniques [6]. In such cases, reconstructive approaches, including local and distal scalp flaps or split thickness skin graft, are often the most suitable options [6]. However, these techniques should be used with caution, as they can be aesthetically altering and are often limited by the scalp's poor elasticity and vascularity [6].

Recent innovative studies suggest a potential link between the use of certain antihypertensive medications and the increased risk for the development of epithelial skin tumors, particularly in the facial/ sun exposed regions [7]. These drugs induce phototoxicity and photocarcinogenicity, concepts that are no longer poorly understood, as increasing evidence continues to emerge in the literature supporting their role in skin carcinogenesis [8,9].

We present two patients with single and multiple tumor formations located in the scalp and auricle regions, which were successfully treated with double hatchet flaps.

Due to the anatomical location of the primary wound defects, specifically on the scalp, these were closed using the double hatchet flap technique.

New and important aspects of the pathogenesis of skin tumors are discussed, including concepts such as drug-induced Nitrosogenesis and Drug mediated Photo Nitroso Carcinogenesis of skin cancer.

Case report-1.

A 70-year-old male presented to the dermatology department with a primary complaint of a gradually enlarging tumor-like lesion on the scalp, persisting for over 4-5 years.

His medical history includes arterial hypertension, for which he is not receiving any treatment. He is currently taking sodium valproate 500 mg administered as two tablets in the morning and one at noon because of complex absence seizures.

The dermatological examination showed a round tumor-like formation with erosion and purulent discharge in the left temporoparietal region of the scalp (Figure 1a,b). Enlarged lymph nodes were not palpable.

Routine blood tests were unremarkable, except for an elevated cholesterol level of 6.09 mmol/l (normal range: less than 5.17 mmol/l).

Following thorough disinfection of the surgical field, the tumor-like formation in the left temporoparietal region of the scalp was excised (Figure 2a). The scalp skin was prepared (Figure 2b), the wound edges were adapted, and the resulting primary defect was closed using a double hatchet flap technique (Figure 2c). The secondary wound defect was closed with single interrupted sutures (Figures 1c and 2d). A Hippocratic cap dressing was applied.

Histopathological examination showed an extensive dermal and subdermal focus of low-risk nodular basal cell carcinoma, characterized by extensive superficial ulceration, minimal desmoplastic stromal reaction, and a well-represented tumor-infiltrating lymphocyte population. The lesion measured 30 mm in diameter and 5 mm in thickness, involving part of the lateral resection margin and extending to within 1 mm of the lower (deep) resection margin, corresponding to the thickness of the underlying skeletal muscle layer it invades. A diagnosis of ulcerative nodular basal cell carcinoma, classified as stage T2N0M0R1, was confirmed. Given the close proximity of tumor cells to one of the lateral resection margins, clinical monitoring and, if necessary, additional histological assessment were recommended.

Case report 1.

A 78-year-old woman presented to the dermatology department with primary complaints of two lesions. The first, a tumor-like formation in the scalp area, was initially noticed approximately 20-25 years ago and had significantly increased in size over the past two years. The second lesion, located on the right auricle, appeared around 15 years ago.

Her medical history included arterial hypertension, type 2 diabetes mellitus, obesity, and a total hysterectomy in 1988. The patient had been on systemic therapy since 1999- 2001 (for 23 years) with bisoprolol fumarate 5 mg half a tablet in the morning and metformin hydrochloride 850 mg half a tablet in the morning and evening. Additionally, she had been prescribed amlodipine/valsartan/hydrochlorothiazide 5/160/12.5 mg once in the evening since 2022 (prior to the consultation in 2024).

The dermatological examination revealed a tumor-like formation located on the scalp, with an irregular shape and nodular structure, measuring approximately 2 cm in diameter (Figures 3a and 4a). It exhibited superficial ulceration with areas covered by yellowish squamous crusts (Figure 4a,b).

The lesion located on the right auricle appeared as a nodular, rounded, well-demarcated pigmented formation, approximately 1.2 cm in diameter (Figure 3a,b). The second lesion was clinically suspicious for nodular melanoma DD pigmented basal cell carcinoma.

A complete CT scan of the body/ head showed no abnormalities.

The two lesions were scheduled for a two-stage surgical excision. In the first stage, the lesion on the right auricle will be removed, followed by the excision of the scalp lesion after the patient had fully recovered.

The lesion in the right auricle was excised under local anesthesia with lidocaine, ensuring a surgical safety margin of 3 mm in all directions. The defect was closed with single interrupted sutures (Figure 3b). Histopathological examination revealed a well-demarcated epithelial lesion characterized by orthohyperkeratosis, epidermal atrophy, and proliferation of atypical basaloid keratinocytes forming nests of varying sizes. These nests exhibited peripheral palisading and were demarcated by a retraction phenomenon from a fibrous, well-vascularized, hemosiderin-rich stroma. No perineural or lymphovascular

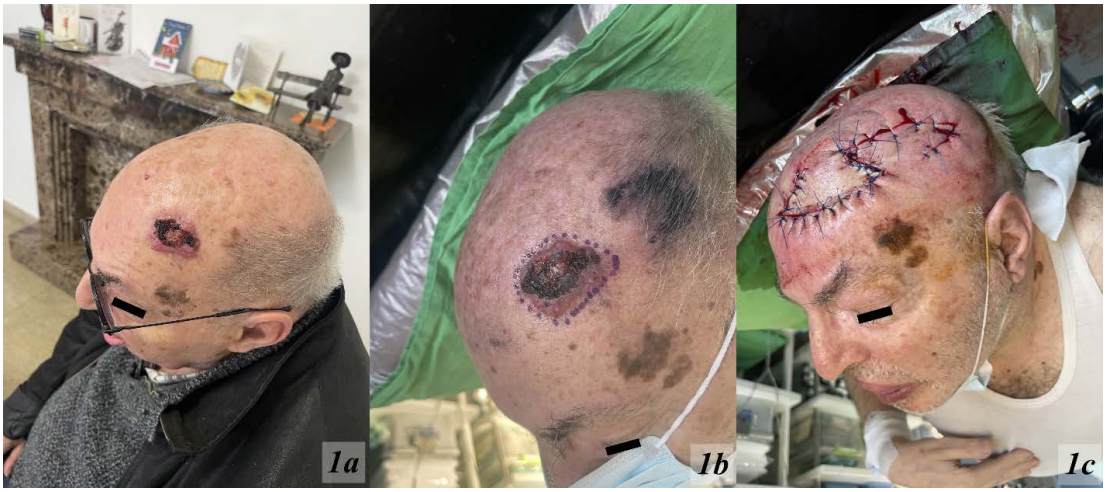

Figure 1a-c. *Preoperative view: A round tumor-like formation with erosion and purulent discharge in the left temporoparietal region of the scalp (a). Intraoperative view: The lesion was marked before the surgical excision (b). Postoperative view: The secondary wound defect is closed with single interrupted sutures (c).*

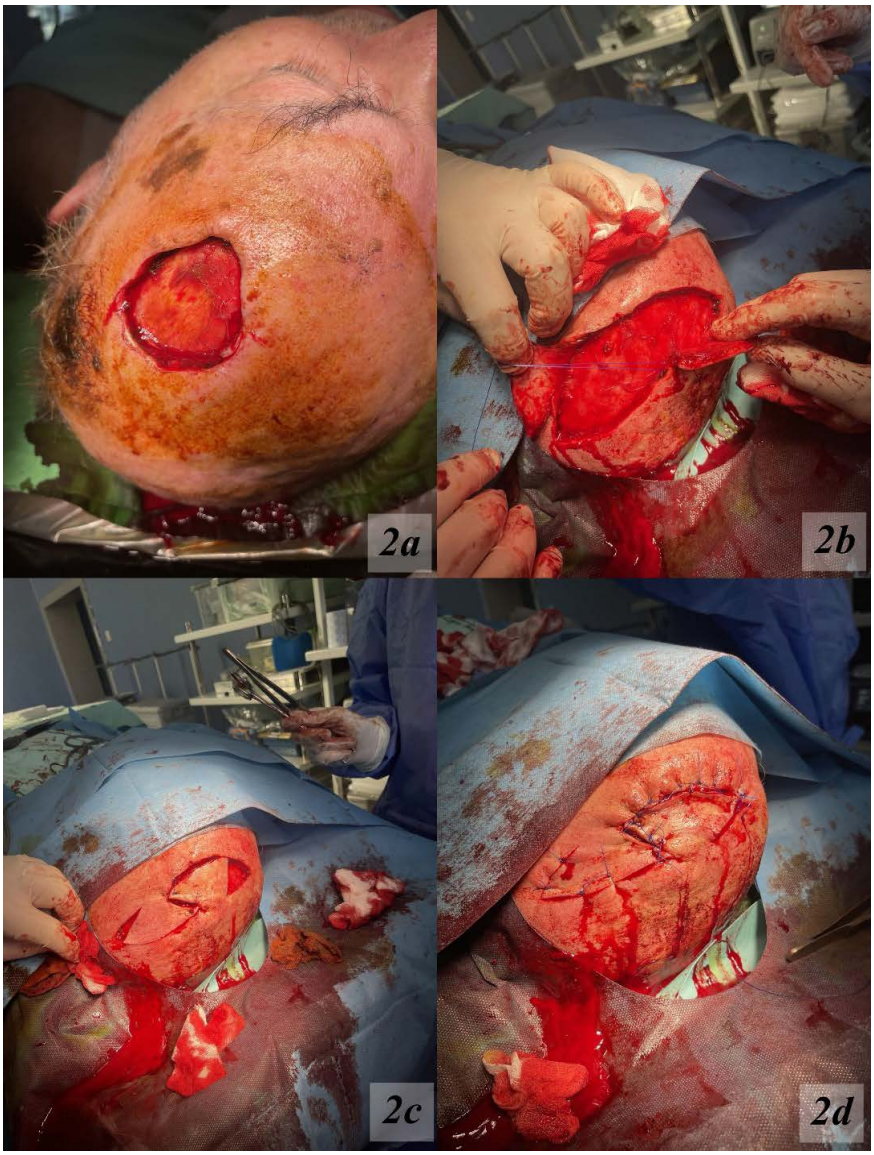

Figure 2a-d. *Intraoperative view: the tumor-like formation in the left temporoparietal region of the scalp is excised (a). The skin of the scalp is prepared (b), the wound edges were adapted, and the resulting primary defect was closed using a double hatchet flap technique (c). The secondary wound defect was closed with single interrupted sutures (d).*

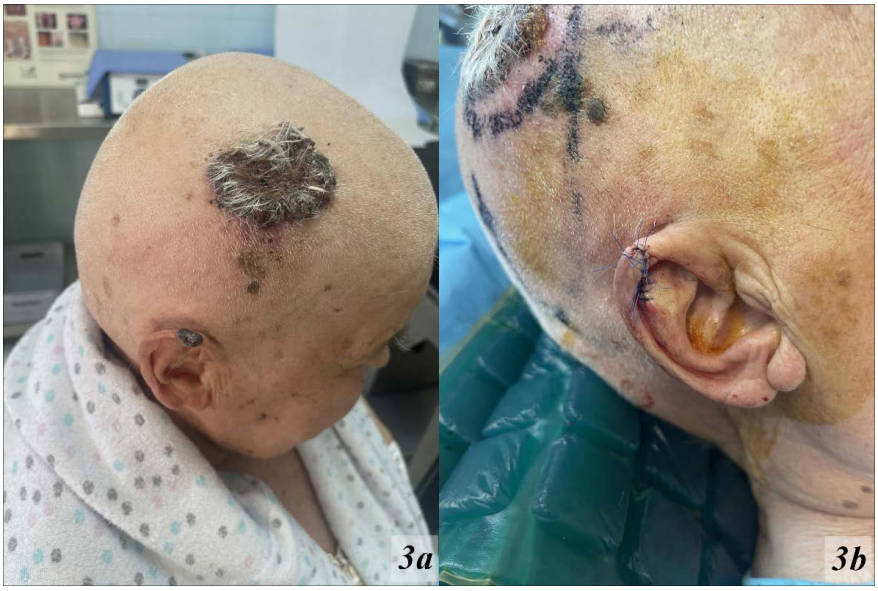

Figure 3a,b. *A tumor-like formation located on the scalp, with an irregular shape and nodular structure, measuring approximately 2 cm in diameter, with superficial ulceration and areas covered by yellowish squamous crusts can be noted (a). A second lesion, located on the right auricle characterized as a nodular, rounded, well-demarcated pigmented formation, approximately 1.2 cm in diameter, can be also noted (a,b).*

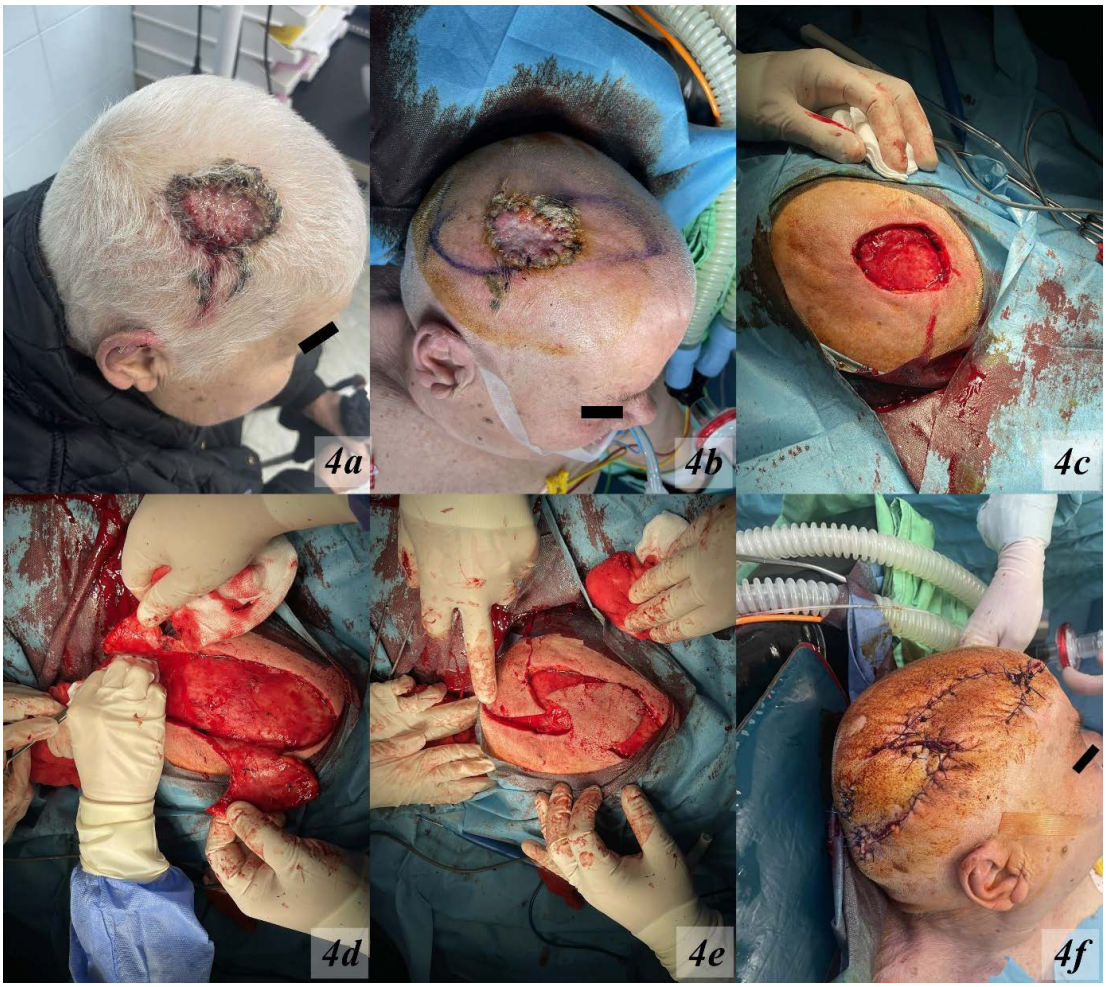

Figure 4a-f. *Preoperative view (a): a tumor-like formation located on the scalp, with an irregular shape and nodular structure, measuring approximately 2 cm in diameter, with superficial ulceration and areas covered by yellowish squamous crusts (a,b). Intraoperative view (b-f): The lesion located on the scalp is excised under local anesthesia, resulting in a circular defect (c), followed by preparation of the flap (d). Closure is achieved using a double hatchet flap technique (e), with single interrupted sutures applied to the secondary wound defect (f).*

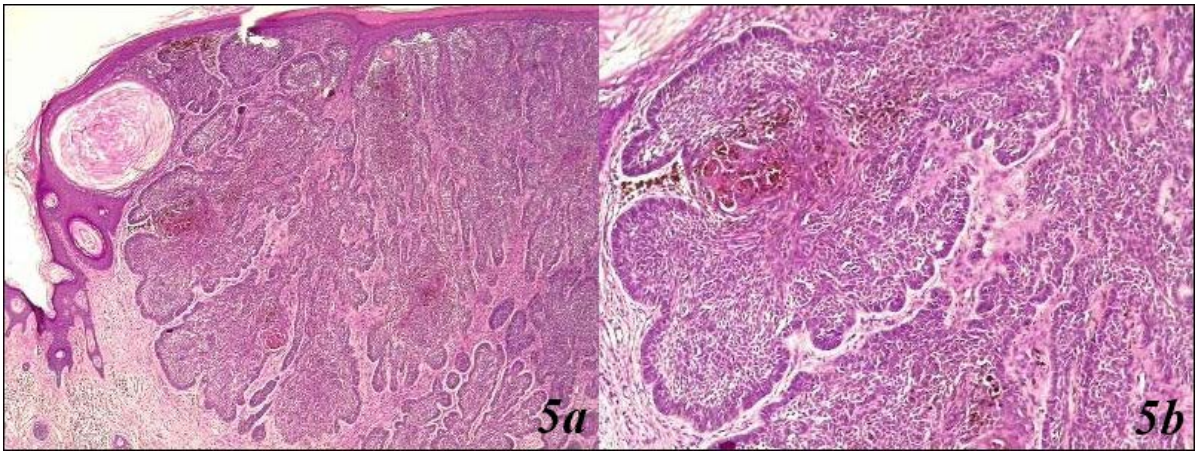

Figure 5a,b. *Histology panel: a well-demarcated epithelial lesion characterized by orthohyperkeratosis, epidermal atrophy, and proliferation of atypical basaloid keratinocytes forming nests of varying sizes. These nests exhibits peripheral palisading and are demarcated by a retraction phenomenon from a fibrous, well-vascularized, hemosiderin-rich stroma. No perineural or lymphovascular invasion is detected, and resection margins are clear.*
5a: *Proliferation of basal cells with hyperchromatic nuclei, forming nests with palisading periphery, encompassed by fibromyxoid stroma with plenty of melanophages.*
5b: *Nests of basal cells of various size, included in fibrous stroma rich in melanophages.*

invasion was detected, and resection margins were clear (Figure 5a,b). The diagnosis was confirmed as pigmented nodular basal cell carcinoma.

The lesion located on the scalp was excised under local anesthesia, resulting in a circular defect (Figure 4c), followed by preparation of the flap (Figure 4d). Closure was achieved using a double hatchet flap technique (Figure 4e), with single interrupted sutures applied to the secondary wound defect (Figure 4f). Histopathological findings confirmed basal cell carcinoma, staged as T1N0M0.

The patient' medication regimen was modified with torasemide 5 mg half a tablet in the morning 2-3 times per week, metoprolol succinate 25 mg in the morning amlodipine/ valsartan/hydrochlorothiazide 5/160 mg once in the evening, moxonidine 0.2 mg at 22:00 if blood pressure exceeds 140/80 mmHg, and rosuvastatin 10 mg once daily in the evening.

Discussion.

The treatment of scalp-associated cutaneous carcinomas presents a significant challenge for dermatologists, as well as plastic and reconstructive surgeons [10]. This complexity arises due to: 1) the restricted tissue mobility caused by the anatomical limitations of the region, 2) limited tissue expandability, 3) a high risk of significant blood loss, 4) the potential for nerve and arterial damage, which may result in necrosis or paralysis, and 5) the challenge of preserving or restoring hair-bearing tissue when necessary [10-13]. Additionally, achieving an optimal aesthetic outcome remains a crucial consideration [12]. These challenges necessitate thorough preoperative planning to ensure successful reconstructive outcomes [10].

The skin of the scalp is highly susceptible to damage, especially from cutaneous neoplasms [14]. The lack of skin elasticity and actinic damage can significantly restrict reconstructive options for defect closure, especially in cases involving medium to large primary defects [14].

Primary scalp defects can be reconstructed using rotation or combined rotation-advancement flaps [14].

For small to medium-sized defects, the double hatchet flap technique is an effective option – this triangular local rotation flap, based on a random vascular supply, enables both rotational and advancement movement for optimal closure, while preserving the cosmetic integrity of the hair-bearing scalp [14,15].

The technique begins with excision of the tumor along with enough surgical safety margins, resulting in a primary circular defect [15]. Primary closure is often not possible due to the anatomical convexity of the scalp, necessitating the need of an appropriate reconstructive approach – in our case, the double hatchet flap [15].

Two opposing reverse hatchet flaps are initially dissected down to the periosteum [16]. When designing the two flaps, the circular defects are measured, and each flap should be approximately 1.5 times the diameter of the defect, with the pedicle width around 0.5 times the diameter of the primary tumour [15,17]. Dissection is carried out in the subgaleal plane, with careful preservation of the vascular supply from the subdermal plexus [14,15]. Once mobilized, the flaps can be rotated, and the distal portion of the defect is then closed in a V-Y pattern [14,15].

The subsequent galeal and cutaneous sutures are then placed [16]. The integration of rotation and advancement movements of both flaps enables the closure of the defect, with the traction forces being evenly spread in two opposite directions from the defect [18]. The flap can be used for reconstruction of defects located not only on the scalp but also on the eyebrow, lower eyelid, nasal tip, cheek, chin, arms, torso, with no reported cases of flap loss [17]. Local flaps on the scalp are the preferable options often because of the ability to hide the final scar in hair-bearing skin, but also the ability to perform wound repair under local anaesthesia [19].

Although the technique is typically reserved for small to medium-sized defects, it was successfully applied to wound defects ranging from 2-5 cm in diameter on the scalp and forehead, similar to our cases, resulting in excellent outcomes

[20]. Its application in larger defects also demonstrates highly favourable results, both functionally and aesthetically [21,22]. The result of the classical double hatchet flap technique transforms a circular defect into an "S" shaped suture line [23].

Challenges such as partial flap necrosis and minimal paralysis have been reported in few cases as postoperative complications, with scarring being the most troubling concern expressed by patients [20].

However, in cases where the size and extent of the defect – particularly those exceeding 32 cm^2 wound defect – make it impossible to close the defect using flaps positioned at 180 degrees to each other, alternative approaches may be required [23]. In such cases, some authors suggest a different modified design of the classical double hatchet flap – arranged in non-opposing configuration rather than the traditional opposing pattern - to cover intermediate and slightly larger scalp defects that cannot be effectively managed with other closure techniques [23]. With this modification, the authors suggest that the classical benefits of the original technique are retained, while the final scar remains well-camouflaged preservation of the natural hairline [23].

To avoid compromising the vascular supply, the pedicle size was maintained equal to the diameter of the wound, while the flap length was extended to twice the wound diameter – compared to1.5 times the wound size in the original technique [23].

In this modification, both flaps share a common base [23]. This technique may be particularly beneficial when the classical method opposing flap configuration is not viable due to compromised scalp vascularity or pre-existing skin damage from prior trauma or surgical procedures [23].

The performance of this kind of severe dermatosurgical manipulations could be avoided if 1) the presence of photo-carcinogens/nitrosamines in the drugs is elucidated or 2) the prerequisites are created for patients and therapists to distinguish contaminated from non-contaminated drug products. The latter currently violates all legal and moral norms in medicine and beyond.

The second aspect that we would like to comment in this scientific paper, is focused on the innovative newly discovered idea concerning the pathogenesis of skin tumors, the so-called drug mediated Nitrosogenesis/Carcinogenesis. Or rhetorically asked: How to avoid severe dermatosurgical reconstructions through plastic surgery ? And: Precisely, by taking into account the new ideas and the new approach in the respective patient groups.

The emerging hypotheses regarding skin cancer pathogenesis/ skin carcinogenesis are also evident/supported in one of the cases presented. The second patient presented with two tumors located in ultraviolet-exposed areas – one on the scalp, initially noticed approximately 25 years ago with a marked increase in size over the past 2 years, and a second lesion on the right auricle, which appeared 15 years ago.

The patient had been on systemic therapy for 23 years with bisoprolol fumarate and metformin hydrochloride. In this case, the development of the scalp tumor was preceded by long-term systemic intake of bisoprolol and metformin – both of which are listed by the FDA as medications with potential nitrosamine contamination [24,25].

N-nitroso-bisoprolol is currently listed under predicted carcinogenic potency category of 4, with recommended AI limit of 1500 ng/day [25]. The scalp tumor appeared two years prior to the initiation of the therapy, with notable progression observed following the start of the systemic therapy.

Similarly, the lesion on the right auricle appeared and progressed during the long-term administration of these medications (approximately 8 years after initiation of the therapy). The patient's condition worsened in 2022 following the introduction of a combined medication containing amlodipine/ valsartan and hydrochlorothiazide. Notably, all three of these medications are also listed by the FDA as potentially contaminated with nitrosamines [25,26].

N-nitroso-amlodipine is currently listed under carcinogenic potency category of 5 with recommended AI limit of 1500 ng/ day and N-nitroso-hydrochlorothiazide is under carcinogenic potency category of 4 with recommended AI limit of 1500 ng/day [25]. In this case, the development and progression of two tumors occurred in the context of long-term use of five potentially contaminated with nitrosamines drugs – metformin, bisoprolol, amlodipine, valsartan and hydrochlorothiazide [24-26].

The carcinogenic potency data of the described drugs are indicative that drugs containing low carcinogenic potency generate cancer via phototoxicity or cumulative phototoxicity. This is where the disconnect/probable reason lies in the insufficiency of the regulator assays: the phototoxic/ photocarcinogenic effect of nitrosamines does not, in all likelihood, correspond to the carcinogenic potency/direct carcinogenic effect, (which ranges between 1 and 5/ as defined by the FDA). The photocarcinogenic effect mediating (photo) carcinogenicity subsequently / in humans could be accompanied by a weak direct carcinogenic effect in bacteria and guinea-pigs (similar to that of hydrochlorothiazide).

Hydrochlorothiazide, which has a lower carcinogenic potency than valsartan, has been determined to be carcinogenic to humans by the IARC. Based on the same logic, it becomes an open question: why IARC does not classify drugs with significantly higher carcinogenic potency than (hydrochlorothiazide) as carcinogenic also for humans (e.g. sartans, which are associated with heterogeneous forms of cancer))? For example, valsartan?

The answer should also be sought in the reasons for the regulators' reluctance to comply with the scientific community, which defined nitrosamines as highly phototoxic substances more than 50 years ago [36].

The avoidance of precise definition of terms such as cumulative photocarcinogenic effect and direct mutagenic/carcinogenic effect has so far helped the regulators to skilfully avoid the essential questions of skin cancer generation. This comfort and blurring of terms should be reconsidered.

Interestingly, sartans and hydrochlorothiazide have drawn significant attention from the scientific community since 2017, due to their strong association with an increased risk of developing epithelial skin tumors [27]. A significant association has been observed between the use of angiotensin receptor

blockers (ARBs, sartans), ACE inhibitors (ACEIs), and thiazide diuretics with the development of both basal and squamous cell carcinomas [27]. According to the data presented by Nardone et al. [27], sartans/ angiotensin receptor blockers use was linked to an increased risk of basal cell carcinoma, with an unadjusted odds ratio (OR) (95% CI) of 2.16 (1.85-2.52) and an adjusted OR (95% CI) of 2.86 (2.13-3.83) [27]. After adjustment, the odds ratios indicate that there is nearly threefold (2.86) increased risk of developing basal cell carcinoma associated with sartan/ angiotensin receptor blocker use [27].

Similarly, thiazide intake was associated with an increased risk, showing an unadjusted OR (95% CI) of 1.73 (1.49-2.02) and an adjusted OR (95% CI) of 2.11 (1.60-2.79) [27]. The odds ratio for thiazide use suggests more than a twofold (2.11) increased risk for developing bcc after thiazide use [27].

The main rhetorical question remains: 1) whether the combination of several medications – specifically a sartan (valsartan) and a thiazide (hydrochlorothiazide) – results in a higher cumulative risk for epithelial skin cancer, particularly basal cell carcinoma but not only, compared to the risk associated with either drug alone; or 2) whether the combined use of all five potentially nitrosamine contaminated medications - metformin, bisoprolol, amlodipine, valsartan and hydrochlorothiazide - although not calculated like the sartans and thiazides in the article by Nardone et al. [27], may pose an even greater risk concerning the skin carcinogenesis?

According to the latest data, hydrochlorothiazide is associated with the development of keratinocyte skin tumors – squamous and basal cell carcinomas due to their photocarcinogenic effects [28]. A retrospective study by Kuntz et al [28] found significantly higher use of hydrochlorothiazide among patients with atypical fibroxanthoma and pleomorphic dermal sarcoma (44.5%), compared to those with squamous and basal cell carcinoma (25.3%). Interestingly, the increased risk for atypical fibroxanthoma and pleomorphic dermal sarcoma was also associated with diabetes mellitus or its related comorbidities [28]. And all of them seems to be related to polypharmacy and polycontamination with NAs.

A Japanese study by Hashizume et al. [29] found that the risk of nonmelanoma skin cancer was significantly higher among hydrochlorothiazide users compared to non-users (hazard ratio, 1.58; 95% confidence interval, 1.04-2.40), with a predilection for sun-exposed areas and tendency toward squamous cell carcinoma development.

Another study by Azoulay et al. [30] concluded that hydrochlorothiazide was not linked with an overall increased risk of keratinocyte carcinoma when compared to ACE inhibitors or calcium channel blockers; however, elevated risks were observed with prolonged use (>= 10 years; hazard ratio: 1.12; 95% CI: 1.03-1.21) and higher cumulative doses (>=100,000 mg; hazard ratio: 1.49; 95% CI: 1.27-1.76). The article also highlights an increased risk not only for keratinocyte carcinomas (but also for melanomas), with phototoxicity identified as the primary underlying mechanism [30].

Additionally, the association between calcium channel blocker use and skin cancer development deserves further attention and should not be overlooked [30].

Higher risk of nonmelanoma skin cancer was observed with the use of antihypertensives (HR [95% CI]: 1.12 [1.07-1.18]), ACE inhibitors (1.09 [1.01-1.18]), calcium channel blockers (1.13 [1.05-1.22]), diuretics (1.20 [1.12-1.27]), loop diuretics (1.17 [1.07-1.28]), and thiazides (1.17 [1.03-1.33]), likely due to drug-induced photosensitivity [31]. The article also demonstrates that the risk increases with the number of antihypertensive medications taken [31], which is reflected in the case of our second patient, who developed not one, but two tumors.

The latest data from our Bulgarian team identifies a link between the intake of potential nitrosamine-contaminated metformin and the development of basal cell carcinoma [32]. They are supported by the recognition and identification of a series of similar cases linking metformin intake, whether in the context of mono- or polymedication, with the development of up to 16 tumors in a single patient [33].

Analysing these events, the presented data seems to be additionally supported by several similar/ identical examples, such as: 1) the following observation (metformin in combination with losartan/hydrochlorothiazide, metoprolol and nifedipine) [33], which could be entirely analogous, involving the same drug classes of medications as in our case (metformin in combination with bisoprolol, and amlodipine/valsartan/hydrochlorothiazide); 2) a second article about another polymedication intake, including gliclazide and metformin, sotalol, bisoprolol, candesartan/hydrochlorothiazide, and lercanidipine [34]; and 3) additional intriguing clinicopathological correlations (metformin, amlodipine, bisoprolol, valsartan/losartan, perindopril/enalapril with additional melitracen, paroxetine, venlafaxine) described by the authors, based on their clinical observations regarding the rising skin cancer incidence [35]. These clinicopathological correlations can be explained by the presence of nitrosamines in the patient's medications, or any described class of drugs, according to the FDA list [25]. The reason for this is likely because, in addition to being carcinogens and mutagens, nitrosamines are also phototoxic substances, a fact that has been known for decades [36]. There is also evidence regarding currently available substances that are both phototoxic and genotoxic, often found simultaneously in a single medication [37,38].

The article by Schmidtsdorff et al. [38] also demonstrates the recently identified presence of multiple nitrosamines in a single tablet, which remains problematic for patients due to the cumulative photo- and genotoxicity of these drugs.

In practice, new concepts such as drug-induced Photo/ Nitrosogenesis and Photo/Nitrosocarcinogenesis are emerging in medicine, particularly in relation to skin cancer [39-41], making them a reality rather than a myth [42]. The near future is expected to provide further insight into the establishment and detailed study of these revolutionary perspectives.

Metformin as a comedication and viewed in terms of 1) nitroso contamination and 2) subsequent development or progression of keratinocytic tumors, remains highly problematic [32-35].

Metformin contamination with nitrosamines is also a regulatory problem. Compliance with the permissible or regulatory-specified concentrations of nitrosamines such as NDMA in

metformin tablets, for example, are not of paramount concern to patients and do not ensure their safety [43]. The reason for this is that the processes that define carcinogenesis in general are dynamic and variable, i.e., the additional presence of nitrite, for example (as an auxiliary factor in carcinogenesis), generates a 40- to more than 100-fold increase in the NDMA concentration of 96 ng permissible in tablets [43]:

These findings suggest that metformin can react with nitrite in gastric-like conditions and generate NDMA [43].

The concurrent intake of 2 to 3 more drugs (bisoprolol, hydrochlorothiazide, and valsartan, for example) in the context of actual polymedication/polycontamination could be viewed as the intake of a cocktail of carcinogens, mutagens, and photocarcinogens at concentrations up to more than 300 times the regulators' allowable intake concentrations of carcinogens for the day.

Precisely because of this fact, we believe that it should not be surprising to anyone that 1) the polycontamination of polymedication of certain patients (even when the carcinogens contained are within the permissible limits) may actually exceed the concentrations allowed by the regulators many times over, and 2) these photocarcinogens could account for the higher incidence of cancer in general, but also of multiple keratinocytic cancers: Basal cell carcinomas in particular as in one of the cases that we present.

Even more worrying is the fact that in certain geographic regions, such as the USA, for example, there are medicinal products on the market that contain NDMA or DMF as a nitroso contamination, in tablet doses significantly in excess of those recommended by regulators [44].

The cost of ″seemingly safe products″ (those in which nitrosamines are within acceptable limits/tablet form) and ″unsafe products″ (those in which nitrosamine concentrations are within the limits set by regulators/tablet form) appears to be practically indistinguishable [44].

Starting from the fact that whether or not the concentration of NDMA in a given tablet, or that with metformin in this case, is within the normal range, in the presence of nitrite-rich food in the stomach, the nitrosamine concentration could exceed 40-100 fold the permissible range and become risky (dynamic conditions/stomach environment) [43].

It is precisely for this reason that only elimination regimens against nitrosamines prove to be safe or salvageable for patients in terms of skin cancer risk.

The International Organization for Research on Cancer (IARC), the Cancer Agency of the World Health Organization (WHO) has evaluated the carcinogenicity of hydrochlorothiazide, voriconazole, and tacrolimus [45] and the results has been published in the Lancet Oncology [46].

1) ″Interaction of the hydrochlorothiazide molecule with ultraviolet radiation leads to phototoxicity [45,46].

2) The Working Group evaluated hydrochlorothiazide, voriconazole, and tacrolimus as carcinogenic to humans (Group 1) on the basis of sufficient evidence for cancer in humans for each agent [45,46].

3) There was sufficient evidence that hydrochlorothiazide causes squamous cell carcinoma of the skin and cancer of the lip in humans [45,46].

4) The evidence was limited for a causal association between hydrochlorothiazide and basal cell carcinoma of the skin, melanoma of the skin, Merkel cell carcinoma, and malignant adnexal skin tumours [45,46]. ″

Data on the available phototoxicity and subsequent photocarcinogenicity of other groups of high blood pressure medications (but not only), published recently, also remain highly concerning with respect to the development of skin cancer in patients worldwide [47].

To date, only a Bulgarian expert collective has found, for the first time and on a global scale, a serious risk of developing solitary and/or multiple forms of skin cancer in the context of polymedication declared by global regulators as potentially contaminated with nitrosamines [22,33-35,41,48].

Bulgarian scientific teams have gone beyond the scholastic framework on the interpretation of the concept of photocarcinogenicity in the context of the intake of antihypertensive drugs and have demonstrated a fully equivalent pattern of keratinocyte cancer formation after the intake of other classes of drugs (belonging by the FDA to the group of drugs contaminated with nitrosamines) [49,50].

Criticism could also be directed at tests by regulators such as the FDA and EMA to determine the carcinogenicity of a particular drug based on the availability of a particular or given nitrosamine(s). This carcinogenicity determined on the basis of statistical tests in rodents/CPCA test and bacteria/Ames Test, the so called ″laboratory carcinogenesis″ could in no way be reciprocal to the actual, dynamic carcinogenesis in humans which is based on the concept of dynamic cumulative phototoxicity/ photocarcinogenicity in the context of simultaneous interaction of multiple mutagens, photocarcinogens or so-called nitrosamines.

According to the most recent literature, drug-induced phototoxicity and its association with skin cancer are in all likelihood very tentative and logical correlations rather than hypotheses [51]. These are pathogenetically based theses and conclusions whose evidentiary value remains difficult precisely because of the official concealment of photocarcinogens in drug preparations (by regulators), despite their availability. ″Human safe carcinogens with phototoxic potential″, after who's official (unregulated) intake the development of single or multiple skin cancers is observed, are in fact concealed.

The fact that radically different classes of drugs are associated with the generation of phototoxicity leads to the conclusion that the unifying factor should or could be only one, or rather one [51]. The photocarcinogens in the drugs or so-called nitrosamines also remain prime candidates for this position [33-35].

Conclusion.

In conclusion, we present two patients: one with a basal cell carcinoma and the other with two basal cell carcinoma formations located in the scalp and auricle regions, both successfully treated with double hatchet flaps. We also discuss the potential relationship between their tumor formation and drug-induced oncopharmacogenesis or Photo Nitroso Carcinogenesis in the context of skin cancers pathogenesis.

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