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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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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

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Abstract.

The pathogenesis of cutaneous tumors has been known for decades yet remains largely unexplained or incompletely understood. The reason for this mystery lies in the concepts of photosensitivity and phototoxicity: how do they arise or what actually causes them? Recently published data in the medical literature link certain nitrosamines such as nitrosomorpholine, for example, to gene and phototoxicity in humans. A number of other nitrosamines analogous in action and structure are found as contaminants in about 300 of the most widely distributed pharmaceuticals worldwide: NDEA, NDMA, NMBA and many others. These contaminated drugs include beta blockers/ bisoprolol/, thiazide diuretics/ hydrochlorothiazide/, antiarrhythmics/ propafenone/, ACE inhibitors/ lisinopril/, but also a number of other drugs which are, according to the FDA, found to have contaminants with a certain carcinogenic potency ranging between 1 and 5. The phototoxicity and genotoxicity of these contaminants, attributed to the pathogenesis of skin tumors, still remain a mystery.

The problems of the intake of the above-mentioned groups of drugs arise mainly on the basis of the official bulletins of the regulatory bodies, namely that: in practice, the intake of polymedication could in many cases also be considered as regular, permanent, long-term intake of contaminants/ carcinogens/mutagens of heterogeneous type, also known as nitrosamines or NDSRIs.

Nitrosamines are genome modifiers in humans and cause acquired mutations. Their concomitant administration in the context of standard, but currently not yet officially declared as contaminated polymedication, would be able to block certain tumor suppressor genes (p53) as well as activate RAS oncogenes. Or in practice- daily administration of a particular combination of drugs could activate the cascades of carcinogenesis regulating the genesis of skin cancer. Precisely because of this fact, it should not be surprising to anyone that the concurrent intake of the aforementioned drugs could also be associated with the clinical manifestation of multiple keratinocytic tumors. We describe a consecutive case of a patient who developed 4 keratinocytic tumors: 2 basal cell carcinomas, 1 keratoacanthoma, and 1 squamous cell carcinoma on a background of potentially contaminated polymedication with propafenone, lisinopril, hydrochlorothiazide, and bisoprolol. Recently published innovative international data on the topic are discussed in the context of concepts such as drug-mediated nitrosogenesis, photonitroso-carcinogenesis and metabolic programming/ reprogramming of the tumor cell.

Key words. Photocarcinogenicity, skin cancer, drug related Nitrosogenesis, Nitroso-Photocarcinogenesis, bisoprolol, propafenone, Lisinopril, HCT.

Introduction.

Skin cancer is among the most prevalent cancers in the Caucasian population worldwide and is primarily categorized into melanoma and non-melanoma skin cancer (NMSC) [1]. Pre-neoplastic lesions, such as Bowen disease and actinic keratosis, along with neoplastic lesions, including basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and Merkel cell carcinoma, fall under the category of NMSC [1].

Basal cell carcinoma (BCC) is a slow growing, locally invasive epidermal tumour, exhibiting a metastatic rate of less than 0.1% [2-4]. It represents approximately 75% of all cases of NMSC [2]. Despite its low metastatic rate, BCC can, in some cases, lead to higher morbidity and mortality rates [3,4]. Most of the remaining NMSC cases are primarily squamous cell carcinoma (SCC), which has higher metastasis rates, ranging from 0.3 to 3.7% [2].

Keratoacanthoma (KA) is a rapidly growing, low-grade cutaneous tumor that typically measures 1-2 cm and has a dome-shaped appearance [5]. Its histopathological characteristics closely resemble those of squamous cell carcinoma [5]. Etiological factors contributing to the development of keratoacanthoma include UV radiation, immunosuppression, the use of BRAF inhibitors, exposure to chemical carcinogens, genetic predisposition (such as mutations in p53 or H-RAS), HPV infection, and recent trauma or surgical intervention in the area [5].

Each year, between 2 to 3 million new cases of NMSC are diagnosed worldwide [6]. Ultraviolet (UV) radiation is directly associated with the development of skin cancer [6]. Depletion of ozone levels reduces the atmosphere's protective filter function, leading to increased solar UV radiation reaching the Earth's surface [6]. Statistically, a 10% reduction in ozone levels is expected to lead to an additional 300,000 cases of non-melanoma skin cancer [6]. Caucasians (with lighter skin types) typically face a significantly higher risk of developing non-melanoma skin cancer compared to darker skin types, primarily due to their lower levels of skin pigmentation [6].

Genetic predisposition can also contribute to the development of certain types of non-melanoma skin cancer [1]. In contrast

to basal cell carcinoma, squamous cell carcinoma can arise from the accumulation of genetic damage, leading to precursor (premalignant) lesions such as actinic keratosis or Bowen's disease, and subsequently to SCC [1,2,7,8]. This process allows for the multifocal development of SCCs, a phenomenon known as field carcerization [1,7,8]. SCC development can be initiated by several mutations in tyrosine kinase receptors, the TP53 gene: RAS/MAPK signaling pathways, and the squamous differentiation network (Notch), among others [1,9-11]. Key components in the BCC carcinogenesis involve suppressor genes and proto-oncogenes such as PTCH1 and SMO (components of the Sonic Hedgehog pathway), the TP53 tumor suppressor gene, and various members of the RAS family [1,12,13].

The literature also suggests an oncogenic potential of certain viruses, such as HPV, EBV, and Polyomavirus, in the development of non-melanoma skin cancer [1].

First-line treatment option for post-surgical defects of the lower leg that cannot be closed primarily or are at risk for excessive tension is Split-thickness skin grafting [14,15]. Considering the expected tension at the anatomical site for our patient, this option was selected as the most appropriate for reconstructing the primary defect.

Despite the well-documented role of genetic predisposition, UV radiation, and environmental factors in skin carcinogenesis, the development of multiple cancerous lesions in the absence of these factors raises questions about the underlying causes of skin cancer in our patient and not only. The etiology in such cases remains unclear, leaving an element of mystery regarding the underlying causes of skin cancer.

Case report.

An 87-year-old female presented to the dermatology department with primary complaints of two lesions located on the right upper limb. The first lesion, approximately 2 years old, is situated on the right forearm, while the second lesion, about six months old, is located on the right palm. Over the past few months, both lesions have exhibited growth, accompanied by pain and itching, and purulent discharge was noted over the last 2-3 days.

The patient reports a history of a histologically proven moderately differentiated basal cell carcinoma in the forehead area, which was removed in March 2024, as well as another tumor-like lesion in the right temple area, removed in 2022.

The patient has been on systemic therapy for arterial hypertension for the past 5 years, taking lisinopril/hydrochlorothiazide 20mg/12.5mg taken once a day, bisoprolol 5 mg once a day, and propafenone 150 mg once a day as needed. Additionally, the patient reports a 20-year history of trigeminal neuralgia, managed with carbamazepine 200 mg as needed and Benfotiamine/Pyridoxine hydrochloride and Cyanocobalamin when needed.

The dermatological examination revealed an undermined lesion with thickened edges and an irregular shape, but clear borders located on the dorsal and palmar surfaces of the right hand. This lesion was partially covered with yellowish crusts (Figure 1). In the right forearm area, a rounded tumor-like lesion with superficial ulceration was noted, covered in places with a hemorrhagic crust (Figure 2). On the left forearm, a protruding rounded lesion, clinically suspicious for seborrheic keratosis, was observed. Additionally, onychomycosis was present on the nails of both the lower and upper extremities, and onycholysis was noted on the third and fourth fingers of the left hand. Enlarged lymph nodes were not palpable.

The patient was recommended surgical excisions of both lesions under local anesthesia.

Under local anesthesia with lidocaine 2%, two elliptical excisions of the lesions on the right upper limb were performed. To fill the defect on the dorsal surface of the right hand (Figure 3), a full-thickness skin mesh graft was taken from the left chest area (Figure 4). The graft was subsequently processed and transformed into a split-thickness skin mesh graft by

Figure 1. *Undermined lesion with thickened edges and an irregular shape but clear borders located on the dorsal and palmar surfaces of the right hand. The lesion is partially covered with yellowish crusts. Clinically suspected for squamous cell carcinoma.*

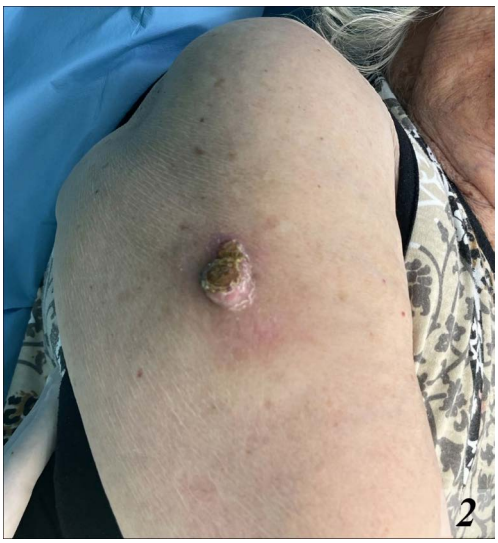

Figure 2. *In the right forearm area, a rounded tumor-like lesion with superficial ulceration is noted, covered in places with a hemorrhagic crust. Clinically suspected for keratoacantoma.*

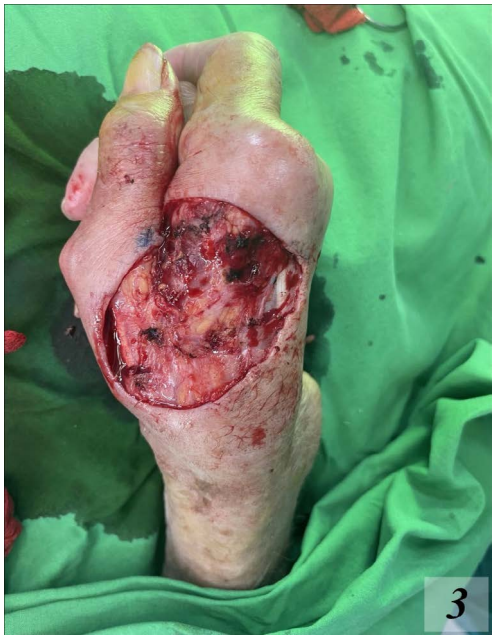

Figure 3. *Skin defect caused by an excision of the tumorous lesion located on the right dorsal surface of the hand.*

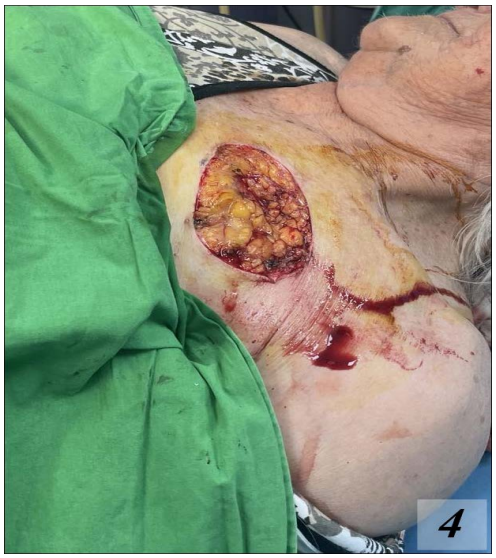

Figure 4. *A split-thickness skin mesh graft is taken from the left chest area.*

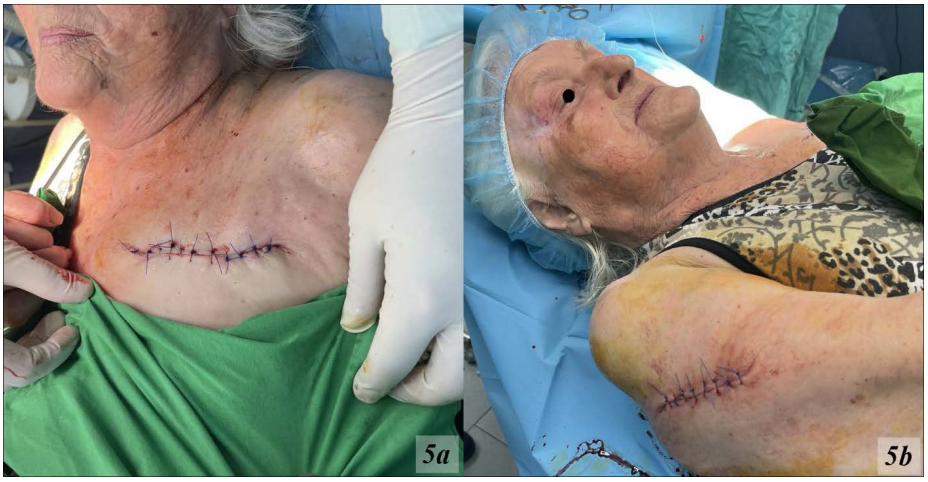

Figure 5. 5a: *The skin edges from the split-thickness skin mesh graft technique were closed with single interrupted sutures* ***5b:*** *The skin defect from the excision on the right forearm lesion was closed with single interrupted sutures.*

excising all subcutaneous tissue and carefully thinning the skin. The skin edges were closed with single interrupted sutures (Figure 5a,b and Figure 6), sterile dressings were applied, and a comprehension dressing was placed on the lesion on the right hand, which was saturated daily with sodium chloride 0.9% solution. Ampoules with metamizole sodium were included in the therapy as needed for pain management. The excised materials were sent for histopathological examination.

The lesion located on the dorsal surface of the right arm was a symmetrical, well-demarcated epithelial lesion characterized by central necrosis and covered with a thick-layered parakeratotic crust. It was demarcated with lateral acanthotic reticulated ridges and had a dyskeratotic base with horn pearls infiltrating the papillary dermis, forming elongated longitudinal projections behind a fibrous, moderately expressed lympho-plasmacytic stroma. There was no evidence of perineural or lympho-vascular invasion, and the resection lines were clear. The lesion was diagnosed as highly differentiated squamous cell carcinoma, staged T1NxMx. A CT scan with contrast of the whole body was further recommended.

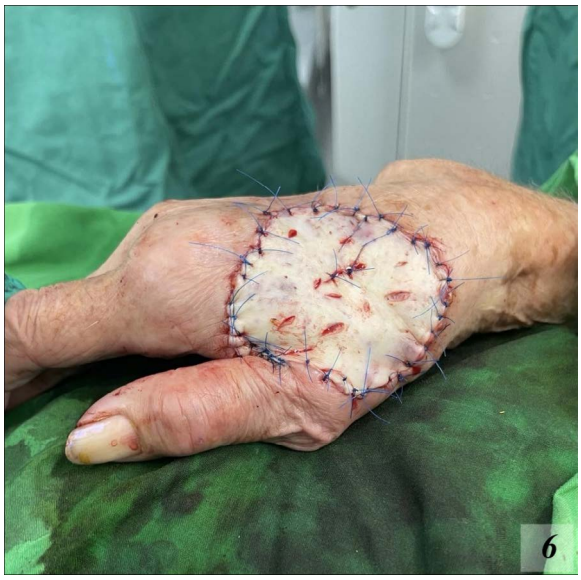

Figure 6. *Split-thickness skin mesh graft transplanted and sutured with single interrupted sutures on the skin defect of the right hand.*

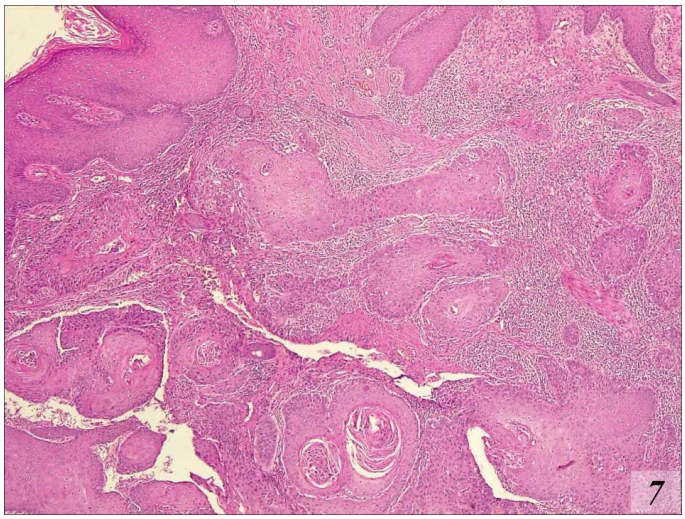

Figure 7. *Keratoacanthoma x 40 x HE.*

The lesion on the right forearm area exhibited characteristics of an extensive, well-demarcated, circumscript epithelial lesion, characterized by ortho- and follicular hyperkeratosis, pseudoepitheliomatous hyperplasia, dyskeratosis, and the formation of "horn pearls". It was demarcated with fibrous, moderately expressed lympho-plasmacytic stroma and exhibited multiple comedo necrosis invading the deep parts of the dermis. There was no evidence of perineural or lymphovascular invasion, and the resection lines were clean. The histological findings corresponded to keratoacanthoma (Figure 7).

The outpatient therapy consisted of ciprofloxacin 250 mg taken twice daily for 7 days, topical dressings with povidone-iodine applied to the lesions on the forearm and chest areas, and an occlusive daily dressings saturated with sodium chloride 0.9% on the hand lesion. Additionally, propafenone hydrochloride 150 mg twice daily, and Lisinopril/Hydrochlorothiazide 20/12.5 mg half a tablet daily, were prescribed.

Discussion.

According to the WHO Classification of Tumours Group [16], keratoacanthoma is considered a distinct diagnostic entity despite its histological and clinical similarities to squamous cell carcinoma [17]. Although the metastatic behavior of keratoacanthoma is controversial, a study by Savage et al. [18], which reviewed 445 cases of KA from 113 published articles (as of 2013), reported no deaths or distant metastases from KA. The statistic was further compared to 429 cases of cutaneous SCC, which reported 61 cases of metastasis and 24 deaths directly resulting from SCC [18]. However, previous articles by Hodak et al. [19] and Piscioli et al. [20] have documented the "metastatic nature" of ″some″ keratoacanthomas.

According to the information gathered by Claeson et al. [17], environmental factors such as UV radiation, male sex, smoking, human papillomavirus, trauma to the skin, immunosuppression, intake of certain medications disturbing the cell cycle and exposure to carcinogens all can contribute to the development of keratoacanthoma.

High UV exposure, along with immunosuppression, are among the main external factors contributing to the development for cutaneous squamous cell carcinoma [21]. Exposure to UV radiation is directly linked to DNA mutations in the transformation-related protein 53 (TP53) tumor suppressor gene [21]. The increased incidence rate for developing not only cSCC but also BCC is associated with UV radiation exposure, especially in individuals with UV radiation-sensitive phenotypes [17,21]. In a cohort study by Dusingize et al. [22], the estimated risk for cSCC was more than twice as high for smokers compared to those who had never smoked (HR, 2.30; 95% CI, 1.46-3.62) [17].

The development and progression of cutaneous squamous cell carcinoma is a complex process marked by mutations in genes responsible for maintaining epidermal homeostasis [23]. This multistage process is further altered by factors such as epigenetic modifications, viral infections, and changes in the microenvironment [23].

Interesting at the moment are the observations of a German team, who associated the use of hydrochlorothiazide with the subsequent development of up to 4 heterogeneous forms of skin cancer: dermal pleomorphic sarcoma, atypical fibroxanthoma, basal cell carcinoma and squamous cell carcinoma [24]. The use of HCTZ was significantly higher in patients with AFX/PDS (44.5%) compared to patients with SCC/BCC (25.3%) [24].

Again, another German collective found a significant association between the use of hydrochlorothiazide and ACE inhibitors with the subsequent development of keratinocytic cancers: squamous cell and basal cell carcinomas of the skin [25].

A pathogenetic association or risk of developing keratinocytic tumors after hydrochlorothiazide intake was found only when there were longer durations of drug intake (≥10 years; HR: 1.12; 95% CI: 1.03-1.21) and higher cumulative doses (≥100,000 mg; HR: 1.49; 95% CI: 1.27-1.76) [26]. Both of the above articles do not comment on which would be able to trigger phototoxicity in practice. Or what could account for this phototoxicity?

According to the most recent literature based on a meta-analysis from 2024, there is a significant association between the intake of photosensitive antihypertensive drugs and the subsequent development of keratinocytic tumors: Increased risks were seen for basal cell carcinoma with calcium channel blockers (relative risk [RR] = 1.17, 95% confidence interval [CI] = 1.11-1.22), diuretics (RR = 1.06, 95% CI = 1.03-1.10), and thiazides (RR = 1.10, 95% CI = 1.04-1.16); for squamous cell carcinoma with calcium channel blockers (RR = 1.08, 95% CI = 1.01-1.14), diuretics (RR = 1.29, 95% CI = 1.17-1.43), and thiazides (RR = 1.36, 95% CI = 1.15-1.61) [27].

Completely overlapping to analogous data are also presented by our patient who developed 2 basal cell carcinomas in the recent past, 1 squamous cell carcinoma and 1 keratoacanthoma (currently) after combined administration of hydrochlorothiazide and lisinopril in combination with bisoprolol and propafenone. It seems that polymedication with potentially nitrosamine-contaminated drugs could correlate with the severity of the clinical picture and/or the number of new tumours.

Similar data from PubMed/ Medline, have focused on the use of photosensitizing drugs in postmenopausal women, and it is these that link 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]) (were each associated) with higher NMSC risk [28].

Combinations of beta-blocker drugs with other potentially nitrosamine-contaminated drugs has been described in the literature repeatedly and again as risky in terms of the development of keratinocytic cancers, including keratoacanthomas [29,30].

As the same data apply with full force to the administration of propafenone and the subsequent development of keratinocytic skin cancers: basal cell and squamous cell carcinomas of the skin [31].

What all newly arising keratinocytic neoplasms have in common with the heterogeneous drugs taken by the patients themselves is their recent cataloguing in the FDA list (2019-2024 period), involving the potential contamination of the latter with nitrosamines/NDSRIs [32].

Another interesting hypothesis of recently published scientific papers [33,34] is based on the claim that polymedication in the context of polycontamination of heterogeneous drug groups could underlie the generation of skin cancer by affecting the so-called metabolic reprogramming or reprogramming of the tumor cell [35].

According to certain relatively new scientific data, nitrosamines localised in tobacco could play a key role in the so-called reprogramming of the future tumour cell (in heterogeneous tumour types), similar to the role of solar radiation - also in this process, but particularly in skin cancer, but in humans [35].

Specific tobacco-localized nitrosamines have been shown to be mutagenic on RAS oncogenes and p53 tumour suppressor gene in humans [36].

The overlap of these target genes with the mutations that are detected in or concerning skin cancer (RAS oncogenes/ p53) are indicative of just such a possible relationship, but this time triggered not by the nitrosamines in tobacco, but by the nitrosamines provided within daily, regular, permanent medication intake.

Antihypertensive monomedication in certain patients could be affected or contaminated by more than 1 carcinogen/nitrosamine [37], which in effect facilitates the activation of metabolic reprogramming of the future tumor cell.

A typical example of a genotoxic yet phototoxic nitrosamine that has been demonstrated in drug preparations is nitrosomorpholine [38].

It remains an open question at present whether the other nitrosamines/nitroso derivatives identified in drug preparations are genotoxic and phototoxic before (analogous to nitrosomorpholine [38]) their metabolisation, and whether, after their metabolisation in the human organism, they still possess a heterogeneous type of carcinogenicity or mutagenicity ?

Even more disturbing is the fact that certain nitrosamines identified as being present in hundreds of drugs, such as NDMA for example, could have a direct activating effect on RAS Oncogenes even before they are metabolized in the liver (39). A different methylated metabolite known as methyldiazonium formed after their metabolization is also mutagenic [39]. In practice, it appears that a nitrosamine such as NDMA could act as a bicarcinogen or polycarcinogen even within the intake of a single drug?

Conclusion.

In conclusion, we describe a patient who developed 4 keratinocytic tumors that developed within the context of a potential nitrosamine contaminated drug regimen with: lisinopril, hydrochlorothiazide, bisoprolol and propafenone. The potential role of drug-initiated nitrosogenesis/photo-nitroso-carcinogenesis/oncopharmacogenesis concerning skin cancer pathogenesis is commented.

Analyzing the clinicopathological correlations of single but also larger groups of patients within the potential polycontaminated drug intake, one could arrive at the following suggestion: polycontamination (with nitrosamines/nitroso derivatives) of polymedication could in all likelihood also be considered as one of the key cofactors for the development and progression of multiple keratinocytic tumors worldwide.

It is for this reason that, one would assume that the introduction of complete elimination regimens for these carcinogens/ mutagens in drug formulations, would have been the most adequate and safe approach with respect to any clinician's ideal goal: the drastic decline in the incidence of skin cancer and keratinocytic cancers in particular.

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