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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 OF SKIN (HUMAN) CANCER- THE HIDDEN TRUTH OF A NEVER-ENDING STORY: NITROSAMINE CONTAMINATION IN OLMESARTAN, VALSARTAN AND HCT AS MAIN RISK FACTOR FOR THE DEVELOPMENT OF KERATINOCYTE CANCER

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Abstract.

The pathogenesis of skin cancer remains shrouded in mystery. Nevertheless, a substantial amount of new data is now available to provide a logical explanation regarding the possible link between 1) the occurrence of single or multiple acquired/somatic mutations and 2) the generation and progression of skin cancer, as well as 3) the potential association of the above two facts with the availability of nitrosamines in drugs for hypertension, diabetes, gastritis, acne, tuberculosis, various other antibiotics, etc.

The nitrosogenesis of skin cancer is slowly but surely being established as a significant concept that cannot be ignored for longer periods of time. It should only be analysed in detail with a view to future prevention for the benefit of public health.

Although this information has been known for decades (but in relation to the development of other cancers), there is still no comparative analysis of the mutations that occur after ingestion of a particular mutagen, also known as nitrosamine. This analysis could to highlight/support or reject to some extent the thesis of the role of nitrosamines and genetic instability leading to the subsequent generation of a malignant cell clone.

The notion of skin cancer nitrosogenesis should become a priority concept very soon, but it should also become an evidential memory, a byword, and an equivalent of the ignorance with which modern civilization has treated its own health for decades within the processes of globalization. It is these processes that include nitrosamines as a major component of the ″medicinal and nutritional menu″ of patients.

It remains unclear at present why regulatory authorities are making endless attempts to legalise the availability of a number of mutagens/human carcinogens in the most commonly distributed medicines worldwide. And to persuade ″others″ that there is no risk from their permanent, controlled and long-term intake.

The newly introduced regulatory norms in practice concern the potential/permissive availability of nitrosamines in a serious number of drugs: drugs with radically different mechanisms of action such as: ranitidine, metformin, ACE inhibitors, beta blockers, thiazide diuretics, sartans, rifampicin, but also probably a number of others.

However, the occurrence of identical, similar patterns of cancers (skin cancers) following their administration (after ingestion of different classes of drugs) makes the ubiquitous permissive availability of nitrosamines (in each class of these drugs) the most potent and most likely pathogenetic inducer of cancer. These comparative patterns of skin tumor occurrence should have even stronger evidentiary value than even so-called prospective follow-ups.

Nitrosamines are and remain one of the best studied mutagens/carcinogens that can alter/modify the human genome. A fact underlined repeatedly over the years (also based on in vivo data, repeatedly ignored) and a fact that, according to the literature, concerns mainly tire industry workers (British rubber workers). It is in this category of patients and after exposure to high doses of nitrosamines (potential inhalation intake) that high mortality has been found in bladder, lung, stomach, oesophageal cancer, multiple myeloma, leukaemia, prostate cancer, pancreatic cancer, and liver cancer. Similar international observations (in vivo/Sweden) concerning intensive human exposure (Swedish rubber workers) to high doses of nitrosamines in a working atmosphere (inhalation type of carcinogen uptake) emphasize the resulting direct subsequent risk of other alarming symptoms such as: nasal bleeds, eye and throat symptoms, hoarseness, cough, nausea, headache, and altered levels of eosinophils and total immunoglobulin G (IgG), compared with unexposed patients.

The neglect of these important observations over the years has led to the ubiquitous and currently difficult to counteract and unpunished prevalence of nitrosamines in even the most commonly distributed drugs worldwide (except in the food industry). It is precisely because of this fact that it should come as no surprise to anyone that there is new evidence of an avalanche in the number of new cancers after intake of potentially nitrosamine-contaminated preparations.

Skin cancer could be seen in the near future precisely as a model of a side reaction after application or long-term contact with mutagens called nitrosamines.

Based on the above, and wishing to add to the worldwide data on the heterogeneous cancers that occur after contact with nitrosamines, we draw the attention of the scientific community to the risk of developing keratinocytic cancer after intake of nitrosamine-contaminated drugs: sartans and thiazide diuretics. We believe that the role of the generic substance in these drugs could also contribute to some extent to the progression of an already present tumour branch, but this influence is rather minor and without significant clinical relevance.

We present a patient who had been taking 2 sartans (valsartan/olmesartan) over the years as monotherapy and in combination with hydrochlorothiazide, who developed over time and within this intake two forms of keratinocytic cancer: verrucous carcinoma and basal cell carcinoma. The focus of discussion concerns a newly introduced medical concept: nitrosogenesis of skin cancer. The detailed study of nitrosogenesis should be a major, primary task for regulators, researchers, clinicians, and

pharmaceutical companies.

Key words. Nitrosamines, olmesartan, valsartan, irbesartan, hydrochlorothiazide, basal cell carcinoma, verrucous carcinoma.

Introduction.

Keratinocytic tumors have been described repeatedly in the world literature as a possible side effect of treatment with sartans as monomedication [1,2], sartans in combination with thiazide diuretics [3,4], but also after monotherapy with thiazide diuretics [5-7]. While in the case of preparations containing sartans and thiazide diuretics and/or thiazide diuretics alone, this side effect could be explained by the possible photosensitizing effect of hydrochlorothiazide, in the case of monomedication with sartans one should also think about the role of additional factors-namely: possible contamination with nitrosamines, for example [1,2].

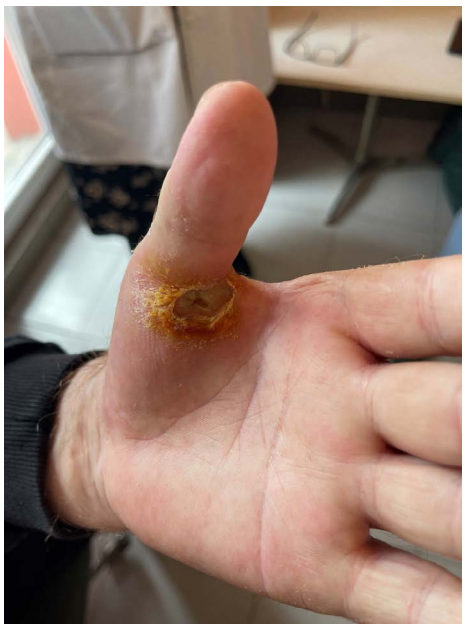
We present a patient who was taking several arterial hypertension medications: valsartan, valsartan/hydrochlorothiazide, and olmesartan, olmesartan/hydrochlorothiazide, and who developed a palmar verrucous carcinoma and a basal cell carcinoma in the neck during this treatment. Possible pathogenetic mechanisms for the staged development of keratinocytic tumors are discussed, with a focus on the current contamination with nitrosamines in high blood pressure medications.

Case report.

A 71-year-old male came to the dermatology department with primary complaints of a persistent pain in the left palm area, due to the presence of a non-healing wound, which occurred after planned radiotherapy in the same area (Figure 1).

Figure 1. *Clinical picture showing a deep ulcerative wound at the site of a verrucous carcinoma removed years ago. Histopathological finding with evidence of postradiation dermatitis.*

In 2015 the patient noticed in the left palm area the appearance of skin formations resembling warts, which gradually began to



grow. He entered another hospital for treatment of the condition in 2018, where the formation was excised, histologically verified as verrucous squamous carcinoma (non in sano), after which he started a course of orthovolt percutaneous radiation, with a total of three courses of radiotherapy in 2018, 2019, and 2022.

In February 2023, he was hospitalized due to an infection of the wound, where incision, lavage and drainage were performed, as well as antibiotic therapy with intramuscular Amikacin 1000mg twice daily for a week, then switched to a reduced dose of 500mg twice daily for another 5 days. During the stay, a CT scan was performed, which ruled out the presence of metastases in connection with the initial tumor of the arm.

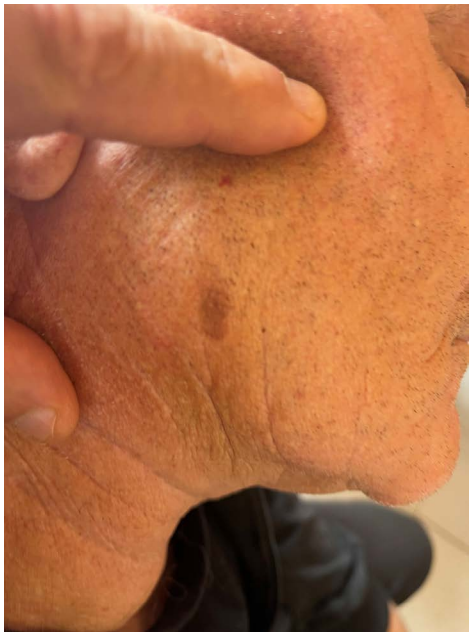
The patient came to the dermatology department due to a persistent ulceration measuring 3.0cm x 3.5cm, located at the excision site of the primary tumor and not healing for 8 months.

In addition, an arterial hypertension without congestive heart failure was diagnosed in 2015, for which he takes the following medications: from 2015 until 2018 – valsartan 160mg once in the morning; from 2018 until august 2022 – valsartan/hydrochlorothiazide 160mg/12.5mg once in the morning; from july 2022 until February 2023 - olmesartan medoxomil/amlodipine 20mg/5mg once in the evening and olmesartan medoxomil/hydrochlorothiazide 20mg/12.5mg; from February 2022 till today – olmesartan medoxomil/amlodipine 20mg/5mg once in the morning; and from 2015 – moxonidine 0.2mg once in the evening when needed.

The dermatological examination showed an ulcerative lesion with raised, whitish hyperkeratotic margins and deep penetration seen in the crease between the thumb and forefinger (Figure 1). Additionally, in the right cheek area, above the mandibula, a plaque with an irregular shape, dark pink color and a pearly edge, was observed, with suspicion for basal cell carcinoma. Enlarged lymph nodes were not palpable (Figure 2).

Figure 2. *Preoperative clinical finding with clinical and dermatoscopic findings suggestive of pigmented basal cell carcinoma of the skin.*

Routine laboratory tests were performed resulting without abnormalities. The ultrasound showed abdominal aorta with pronounced calcinosis and uneven outlines and iliac arteries with



uneven outlines. Pronounced atheromatosis was established. The patient was recommended a change in the regime after the

surgical intervention: a medication that keeps the veins healthy, elastic and toned and clopidogrel 75mg.

Under local anesthesia, the patient underwent surgical excision of the supramandibular tumor-like formation on the right cheek area. Single interrupted sutures and adaptation of the wound edges were performed (Figure 3). Iodacept povidone dressings were made. The histopathological verification showed superficial multifocal basal cell carcinoma measuring 12/1mm, staged T1N0M0. Due to a suspicion of tumor recurrence of verrucous carcinoma in the palm area, two additional biopsies of the lesional skin were performed, resulting in a profuse parakeratosis with serous lacunae, horizontally alternating with compact orthohyperkeratosis, uniform acanthosis with moderate spongiosis, artificial intraepidermal clefting, densely chialinised papillary dermis with coagulation necrosis, obscuring the dermo-epidermal border. The histological constellation demonstrated sclerodermiform changes in the clinical context of chronic radiodermatitis.

Figure 3. *Postoperative clinical finding after removal of basal cell carcinoma in the neck.*

A change in the systemic therapy for the arterial hypertension was recommended with Verapamil hydrochloride 240mg once

daily, spironolacton 50 mg once daily in the morning and doxazosin 4 mg once daily.

Discussion.

The problematic availability of nitrosamines in general, or their increased availability, stems from the fact that whether they are found in ranitidine, metformin, sartans, or thiazide diuretics, it is more than evident that they possess mutagenic activity and potentiate the generation of skin cancer [8,9].

Analogous data are found in their possible presence in ACE inhibitors such as enalapril and perindopril- single or multiple basal cell carcinomas, some of them metatypic [10,11].

It should be noted that these manifestations and associations-namely, between drug intake, potential/(currently actual and EMA-allowed) nitrosamine contamination, and keratinocytic cancer formation-could by no means be defined as sporadic.

There is evidence in the literature of the development of keratoacanthoma and verrucous carcinoma after the intake of a potentially/actually nitrosamine-contaminated combination preparation containing irbesartan and hydrochlorothiazide [12,13].

The occurrence of giant acral melanoma in combination with multiple verrucous carcinomas has also been described in the setting of olmesartan and valsartan therapy [14].

Monotherapy with valsartan , as well as the combination with a thiazide diuretic potentially/actually contaminated with nitrosamines, could lead to the manifestation of basal cell carcinomas [15,16].

Nitrosamine contamination continues to be a huge yet unsolved problem. More and more different classes of drugs appear to be affected by this contamination, and the exact mechanisms of its occurrence are unclear. This is what makes it difficult to eliminate this problem.

Pharmaceutical giant Pfizer is recalling certain lots of INDERAL LA (Propranolol hydrochloride) as early as 2022 due to nitrosamine contamination/ N-Nitroso propranolol/ and risk of cancer development [17]. Thus, betablockers also enter the group of drugs with permissive availability for nitrosamines. It is expected that this particular relationship will soon be thematized similarly to the others mentioned so far concerning ACE inhibitors, sartans and thiazide diuretics.

Thus, in practice, ACE inhibitors, thiazide diuretics as monotherapy or in combination with ACE inhibitors/ or with sartans, as well as sartan monotherapy, could be a risk factor with respect to the development of keratinocytic skin cancer [3-5,6,10,11-15]. The nitrosogenesis of skin cancer should become one of the most significant concepts in the near future, which will provide answers not only to the processes leading to the generation of keratinocytic tumors and melanoma, but also to a number of other cancers.

There is also no shortage of strong evidence from various European follow-up studies highlighting 1) the risk of developing/high mortality from tumours such as prostate cancer, pancreatic cancer, liver cancer, bladder tumours, lung cancer, stomach cancer, oesophageal cancer, multiple myeloma, leukaemia, following inhalation (in vivo) exposure to nitrosamines in occupational settings [18].

Other international observations (Sweden), again concerning intensive exposure (in vivo) of human subjects (Swedish rubber workers) to high doses of nitrosamines in a working atmosphere, emphasize the resulting direct risk of other severe symptoms: nosebleeds, eye and throat symptoms, hoarseness, cough, nausea, headache, and changed levels of eosinophils and total immunoglobulin G (IgG), compared with unexposed

patients [19].

The reason that led regulators to announce a permitting regime for nitrosamines in drugs remains, to date, a huge mystery. Similarly, the reason that led these same authorities to declare that the role of nitrosamines as human carcinogens was currently controversial?

As early as 12 years ago, it was found (in vivo) that intake of high doses of nitrosamines in various forms was associated with a significant risk of developing rectal cancer [20].

Similar and confirmatory results have been reported by a French collective that associated NDMA-contaminated valsartan with an increased risk of melanoma and liver carcinoma (in vivo) [21].

There is also no shortage of single clinical observations that similarly associate the development of colon cancer and melanoma simultaneously after intake of potentially nitrosamine-contaminated sartans and/or hydrochlorothiazide (in vivo) [22,23].

Recent clinical trials' attempts to shift the blame for the development of keratinocytic cancers and melanoma to its known photosensitizing action alone [5] should not divert clinicians' attention from the availability of nitrosamines in high blood pressure medications.

These studies in no way provide an explanation for the development of similar to completely analogous variants of skin tumors that developed in the context of monotherapy with sartans or metformin, for example [1,2,8,11], where the link could be only one: the permissive availability of nitrosamines.

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