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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 CANCER: THE NITROSAMINE CONTAMINATION IN THE CALCIUM CHANNEL BLOCKERS (AMLODIPINE), BETA BLOCKERS (BISOPROLOL), SARTANS (VALSARTAN/LOSARTAN), ACE INHIBITORS (PERINDOPRIL/ENALAPRIL), TRICYCLIC ANTIDEPRESSANTS (MELITRACEN), SSRIS (PAROXETINE), SNRIS (VENLAFAXINE) AND METFORMIN: THE MOST PROBABLE EXPLANATION FOR THE RISING SKIN CANCER INCIDENCE

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Abstract.

The Nitrosogenesis of skin cancer is a newly introduced concept in medical science, the significance of which is yet to be the subject of detailed analyses and discussions. Contamination of the most commonly used drugs for systemic treatment worldwide (such as Angiotensin receptor II blockers/ ARBs, ACE inhibitors, Beta blockers, Thiazide diuretics, Metformin, Ranitidine, Nizatidine, tricyclic antidepressants, anticoagulants/ dabigatran, Rifampicin, calcium channel blockers , SSRIs/ selective serotonin reuptake inhibitors, Varenicline) is already a fact and is more than worrying but also indicative. It is ″this relationship″ that has been repeatedly described in the medical literature (initially) as an association, and subsequently now increasingly as a causal relationship, a pathogenetic relationship.

Observational data from clinicians over the past year increasingly speak in favour of a pathogenetic link and associate every single drug declared as contaminated with the development of heterogeneous forms of skin cancer gradually and surely. New drugs are added monthly that have not yet been declared as actually/potentially contaminated but are probably known to regulatory authorities or are in the process of being clarified. In parallel, the number of nitrosamines identified as contaminants in medicines is growing. This should not be surprising to anyone: ″You take 3 drugs contaminated with mutagens- you subsequently develop skin cancer″.

Polymorbidity and multimedication against the background of polycontamination with nitrosamines appears to be the most serious problem at present. While until recently polymorbidity was considered to be a key factor in carcinogenesis (generator, trigger, inducer), today this dogma should be re-examined or looked at from another, radically different angle: from the angle of polycontamination to multimedication within polymorbidity. It is this that could provide a good explanation for the pandemic concerning skin cancer, for example.

The development of relatively identical patterns of manifestation of skin tumors after concomitant intake of drugs declared as contaminated (drugs from the classes already mentioned above/ with radically different mechanism of action) supports unequivocally the thesis that: the nitrosogenesis of skin cancer is an undeniable fact that should be studied in detail. Studied because it could be eliminated.

The analysis presented within this scientific thesis concerns 4 polymorbid patients who developed skin tumors within the framework of the multimedication they were assigned. The concomitant intake of medications declared as contaminated (in the presented patients) led to the manifestation of single or multiple skin neoplasms that were successfully treated surgically.

Once again, the importance of potential/actual contamination of beta blockers, ACE inhibitors, oral antidiabetic drugs, and sartans in the generation of 1) non-melanocytic forms of skin cancer, and 2) melanoma precursor lesions or so-called dysplastic moles is established and validated.

The possible contamination with nitrosamines of 1) other types of tricyclic antidepressant- Melitracen; 2) antidepressant of the selective serotonin reuptake inhibitor (SSRI) class: Paroxetine; 3) antidepressant of the serotonin and noradrenaline reuptake inhibitor (SNRIs) class: Venlafaxine, as well as of the systemic anticoagulant: apixaban is highlighted for the first time in the world literature.

Key words. Nitrosogenesis, amlodipine, perindopril, enalapril, melitracen, venlafaxine, paroxetine, metformin, BCC, dysplastic nevi, trichoadenoma, metatypical BCC, SCC, Drug induced cancer.

Introduction.

The ubiquitous distribution/contamination of the most commonly used medicinal products worldwide with nitrosamines is, in practice, still a serious problem [1].

The lack of adequate control of the intake of a relevant carcinogen, mutagen, or nitrosamine, as well as the calculation to determine the risk of developing a given cancer subsequently, is determined precisely by the possibility that a given tumor inducer may be further uncontrollably taken up within the feeding process as well [2]. The relationship between the intake of certain types of foods and the development of heterogeneous cancers has been established repeatedly in the past and also remains a dilemma to this day [3-7].

Analogous to this dietary intake, from now on it would be appropriate to calculate the drug intake as well, since nitrosamines of different types (but also of analogous/equivalent type to those in foods) have been found in a number of drug preparations [1,8].

In practice, there is evidence of an association of nitrosamine intake within the dietary process and subsequent development of various cancers in humans. However, when the same nitrosamines (or NOCs/Nitroso Compounds) are found in drugs, the recommendations of regulatory authorities are : That drug intake should not be discontinued, as there is no evidence of carcinogenic effects of nitrosamines in humans? These calls from the regulatory authorities remain to resonate today as a paradox.

Nitrosogenesis of skin cancer is the new, logically sound,

and at present categorically irrefutable concept that links heterogeneous (nitrosamine-contaminated) drug intake to the development of skin cancer [9].

A series of patients with heterogeneous forms of skin cancer that developed after receiving heterogeneous medications that have so far been declared as nitrosamine-contaminated drugs by regulatory authorities worldwide is presented.

Case 1. Keratoacanthoma and dysplastic nevi after Bisoprolol, Amlodipine/Valsartan

We report a 76-year-old patient with complaints of approximately 4 months' duration, manifesting as a tumor formation in the scalp (Figure 1a). According to the patient's history, there is evidence of one painful sunburn in the scalp and body area in adolescence. The dermatological examination revealed clinical evidence of a nodular lesion in the scalp area with a diameter of no more than 1 cm, with a centrally located hyperkeratotic ″ type of tumour″, clinically suggestive of keratoacanthoma (Figure 1a), as well as multiple actinic keratoses (Figure 1a).

Additionally, two nevi with indistinct borders and irregular shape were observed in the dorsal region, one located medially at the level of C7, the other in the left shoulder region, clinically/ dermatoscopically suspicious for dysplastic nevi (Figures. 1b, 1c,1d).

As comorbidities in the patient are known:

Arterial hypertension of 15 years' duration and benign prostatic hyperplasia. The patient's concomitant medications include 1) Bisoprolol fumarate 2.5 mg once daily for 10 years, 2) amlodipine/valsartan 5mg/160 mg once daily for 10 years, 3) moxonidine 0.3 mg once daily in the evening one tablet, and 4) dutasteride/ tamsulosine hydrochloride 0.5mg/ 0.4 mg once daily.

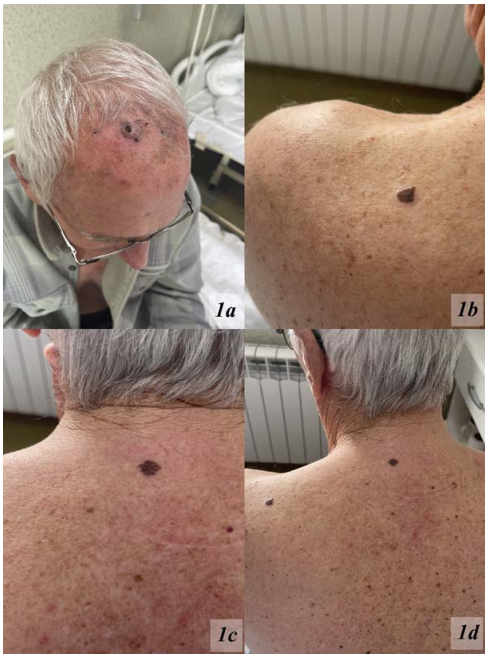

Figure 1. 1a: *Clinically suspicious keratoacanthoma formation in the scalp area.*
1b-d: *Dysplastic melanocytic nevi localized in the upper part of the back.*

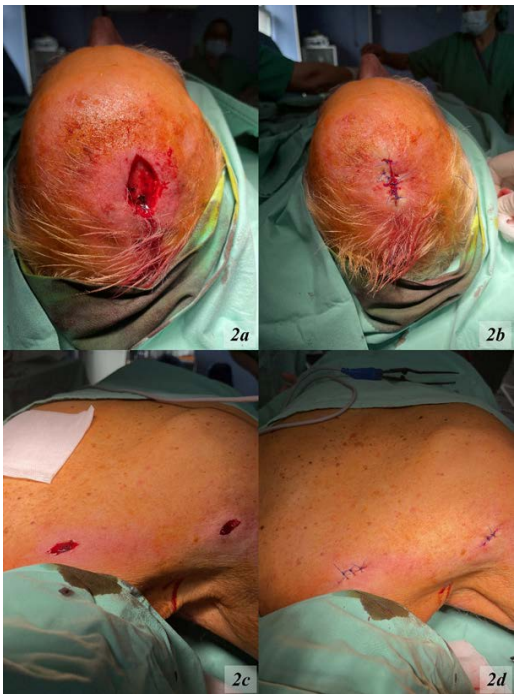

Figure 2. 2a,b: *Surgical removal of the lesion in the parietal scalp by elliptical excision.* ***2c,d:*** *Surgical removal of 2 pigmented dysplastic nevi by elliptical excision.*

Surgical treatment was performed under local anesthesia, and the lesions were removed by elliptical excisions and the defects were closed by stretch plasters and wound edge adaptation by single skin sutures (2a-2d).

Case 2. Multiple basal cell carcinomas in the context of taking bisoprolol, amlodipine, valsartan.

We report a 69-year-old patient who visited the dermatological surgery outpatient clinic due to the appearance of painful tumor formations localized in the skin area, which had been increasing in size in recent months and were causing severe discomfort in the form of burning, itching and increased sensitivity - spontaneously and on touch (Figures 3a-3d).

The tumor formation in the back area dates back to 2015/2016 (Figure 3a,3b), and has progressively increased in size and at times bled over the past 2 years. According to history-taking data, the initial size of the tumor was the size of a bean, was initially asymptomatic and did not make an impression on the patient until mid/late 2020.

The lesion , localized to the shoulder region , appeared (according to anamnestic data) in 2019 and also increased in size progressively over the last 2 years (Figure 3c).

The tumor in the nasal region is present since 2022 (Figure 3d).

Arterial hypertension and heart failure are known as comorbidities in the patient. Systemic medication at the time of hospitalization included: 1) Bisoprolol fumarate 5 mg (twice a half tablet per day from 2018 to date), 2) Amlodipine 5 mg (twice daily from 2019/ morning and evening one), 3) Torasemide 10 mg (one per day from 3 years), 4) sacubitril/ valsartan 49mg /51mg (once daily since 3 years till date), 5) amiodarone hydrochloride 150mg (½ tablet daily since 5 years excluding Friday , Saturday and Sunday), 6) empaglifozin 10mg one tablet daily since 5 months.

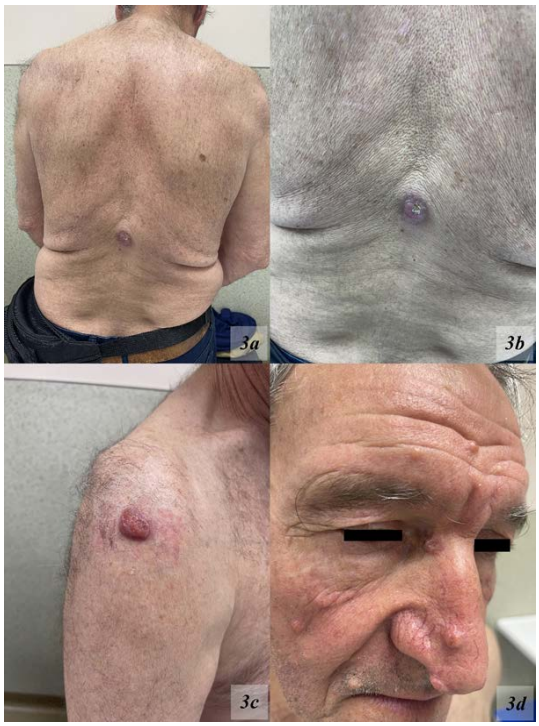

Figure 3. 3a,b: *Epithelial skin tumor in the back area.* ***3c:*** *Nodular tumor formation in the right shoulder area.* ***3d:*** *Basal cell carcinoma in the medial orbital area on the right.*

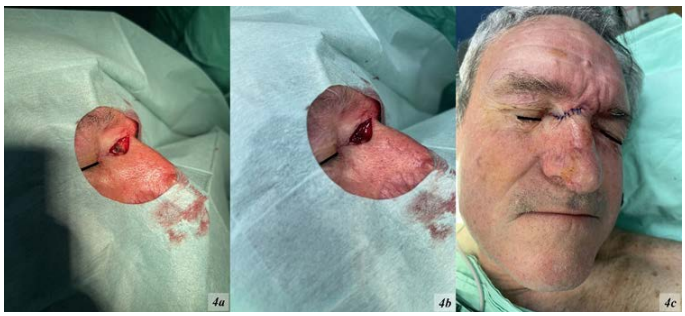

Figure 4. 4a,b,c: *Surgical removal of facial tumor by elliptical excision and staged coverage of the defect by single skin stitches.*

Figure 5. 5a,b,c: *Surgical removal of the tumor in the right shoulder area by elliptical excision - in depth to the musculature 5a,5b.*

The lesions were surgically removed under local anesthesia as the histopathological findings for all three tumors were in favor of adenoid cystic basal cell carcinoma, early stage (Figures 4a-4c/5a-5c/6a-6c).

In the lesion localized in the shoulder region and the one localized adjacent to the medial orbital angle, the resection lines found postoperatively (histopathologically) were close to the tumor cells; therefore, close monitoring of the patient and, if necessary, re-excisions were recommended.

Case 3. Basal cell carcinoma within combined systemic treatment with perindopril, enalapril, losartan, metformin, paroxetine/ SSRIs, melitracen/ tricyclic antidepressant

We report a 67-year-old female patient with a duration of complaints between 3 to 5 months regarding the appearance of a neoplasm , localized in the nasal area (Figure 7a). Clinically, a tumor-like formation with a central ulceration and a pearly border with a diameter of no more than 1 cm , localized to the right of the dorsum of the nose, clinically suggestive of basal cell carcinoma, was observed during the dermatological examination (Figures 7a/7b).

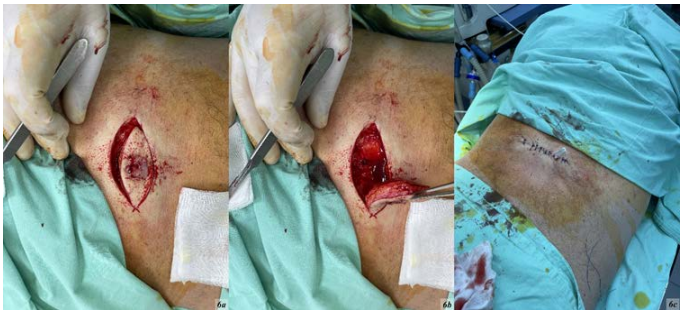

Figure 6. 6a,b,c: *Surgical removal of the tumor in the back area, posterior sweat groove by elliptical excision - in depth to the musculature 6a,6b. Postoperative findings after glove drain placement -6c.*

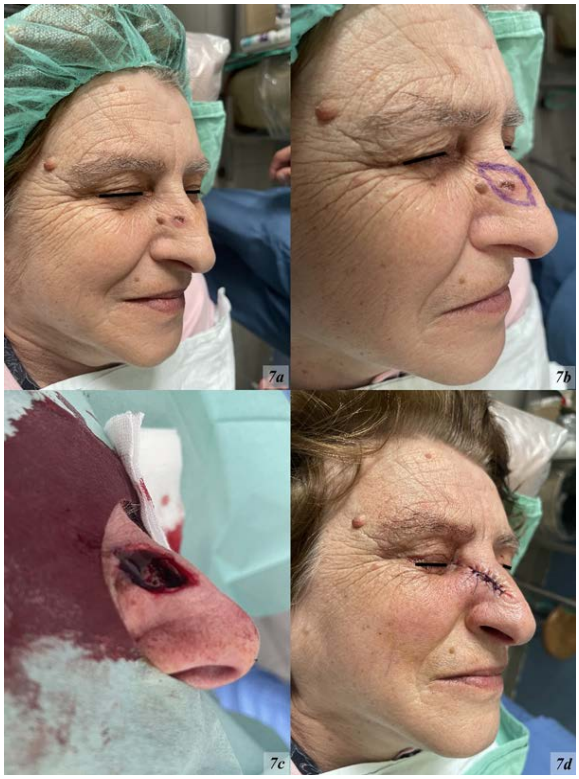

Figure 7. 7a: *Clinical finding with tumor lesion localized in the nasal area, suggestive of epithelial skin tumor/SSC.* ***7b:*** *Preoperative marking of the resection lines.* ***7c:*** *Intraoperative finding - tumor removal by elliptical excision.* ***7d:*** *Immediate postoperative finding after closure of the defect.*

The patient's known comorbidities included a hypertensive heart without congestive heart failure, non-insulin-dependent type 2 diabetes mellitus, and an anxiety disorder.

The patient's concomitant medications include: 1) Perindopril arginine 5mg/ indapamide 1.25 mg/ amlodipine 5 mg, one tablet daily from 2023 (2015-2020 she took Enalapril maleate , 2 times one tablet, subsequently losartan potassium/ hydrochlorothiazide 50/12.5 mg one tablet per day for the period from 2020-2022); 2) Gliclazide 60 mg one tablet in the morning; 3) Metformin hydrochloride 1000 mg for 11 years : half a tablet in the morning and at lunch and one tablet in the evening; 4) Paroxetine 20 mg/ SSRIs/ selective serotonin reuptake inhibitors : one per day for 3 years, and 5) Flupentixol 0.5 mg/ Melitracen 10 mg : 2 tablets per day for 3 years.

Undergone hysterectomy in the past for massive uterine prolapse and a condition after a bout of purulent mastitis years ago.

Inpatient laboratory investigations showed mildly elevated glucose : 6.7mmol/L; hyperuricaemia : 410 µmol/L; CRP 8.6 mg/L; gamma glutamyl transferase /GGT : 60 U/L and massive bacteriuria with isolated Klebsiella pneumonia, subsequently treated with Levofloxacine 5mg/ml once daily for 7 days, intravenously.

The tumor lesion was surgically removed under local anesthesia as an elliptical excision (Figures. 7b/7c/7d), with histopathologic verification of nodular basal cell carcinoma less than 2 cm in size. Histopathological data showed that one lateral resection line was adjacent to the tumor cells. Close clinical monitoring of the patient and re-excision if necessary was recommended.

Case 4. Basal cell carcinoma, trichoadenoma and dysplastic nevus after bisoprolol, venlafaxine (SNRIs/ serotonin and noradrenaline reuptake inhibitors), apixaban (?)

An 86-year-old patient presenting to the outpatient clinic for a wound , localized in the nasal area, which was dated 2017 (Figure 8a). No evidence of intense sun exposure over the years or of painful sunburns in adolescence. Lack of familial predisposition to skin cancer.

Preoperative biopsy was taken on an outpatient basis and was suggestive of basal cell carcinoma. Within the dermatological examination performed, the presence of

1) an ulcerative lesion over the ala nasi on the right with a size of 2.5 cm, central ulceration and a slightly raised peripheral margin, single telangiectasias, clinically suggestive of basal cell carcinoma (Figure 8a), was remarkable.

2) a circular solid tumor-like lesion with a diameter of 1 cm and the presence of dilated blood vessels on the surface, again clinically suggestive of basal cell carcinoma (Figure 8c)/age of the lesion of 2021 was found in the forehead area, frontal left.

3) Temporally on the right, a pigmented lesion with clinical and dermatoscopic features of dysplastic nevus was found (Figure 8b): irregular shape, mild elevation of the lesion in places, disrupted melanocyte network dermatoscopically/ unclear duration according to anmnestic data but change in shape and intensity of pigmentation in the last 2 years.

4) In the dorsal- posterior sweat trough area , at the level of Th 12 as well as two and a half feet to the right , lateral

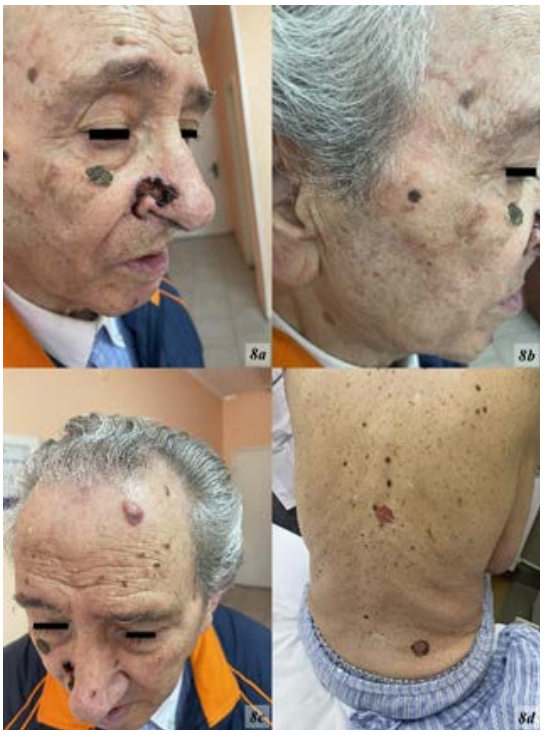

Figure 8. 8a: *Ulcerative lesion subsequently verified histopathologically as basal cell carcinoma involving the ala nasi.* ***8b:*** *Melanocytic nevus histologically identified postoperatively as having mild dysplasia.* ***8c:*** *Trichoadenoma in the forehead area, preoperative finding.* ***8d:*** *2 lesions clinically suggestive of Morbus Bowen, planned for surgical intervention as part of a future hospitalization.*

to the midline, there are 2 lesions , suggestive of cutaneous precancerous lesions (Figure 8d)/ the date of presence of the lesions is over a year, but according to the anamnestic data, which is inconclusive/indicative, cannot be determined with precision: 4. 1) a circular plaque-shaped lesion with red color, fine desquamation, slightly erosive surface and a diameter of no more than 2.7 cm, suggestive of Morbus Bowen (Figure 8d), and 4.2) a lesion similar in shape and size , but localized in the sacral region on the right, suspicious for a pigmented form of Morbus Bowen (Figure 8d).

As co-morbidities are known: Arterial hypertension and permanent atrial fibrillation of at least 10 years' duration; chronic viral hepatitis D without delta agent/ 2023; renal cysts ; degenerative changes of the spine; chronic congestive heart failure; moderate mitral insufficiency ; intermittent left femoral block ; chronic pancreatitis, colonic diverticula ; cavernous hemangioma and liver cysts ; antral erythematoexudative gastritis ; prostate adenoma ; L4/L5 disc herniations ; depression ; chronic insomnia.

The patient's systemic medication within the hospitalization included: 1) bisoprolol fumarate 5 mg: 2 times half a tablet from 10 years, 2) digoxin: 1 time daily half a tablet, 3) apixaban 5 mg : 2 times half a tablet from 2/3 years, 4) esomeprazole 40 mg : once daily half a tablet / from 2 years, 5) olanzapine 5 mg : half a tablet daily from 6 years, 6) venlafaxine 75 mg / SNRIs: 2 times one tablet daily / from 6 years, 7) pregabalin 75 mg: one tablet daily / from 6 years, 8) bromazepam 3 mg: in the evening one or half a tablet, every 2 days / from 30 years, 9) quetiapine

25 mg: in the evening , one to 2 tablets, every 2 days / from 5-6 years, 10) zopiclone 7.5 mg: one half to one tablet every two days / from 1 year.

Preoperative nuclear magnetic resonance imaging of the lesion in the nasal area showed no bone or cartilage involvement.

Three lesions were removed during hospitalization: the first one, located in the nasal area/ with postoperative histopathological evidence of basal cell carcinoma (T2N0M0), clean resection lines, and a flap was performed to cover the defect; 2) the tumor , localized in the forehead area, was histopathologically classified as trichoadenoma, clean resection lines; 3) the pigmented lesion on the right temporal was histopathologically determined as melanocytic nevus with mild dysplasia.

Surgical removal of the remaining two lesions in the dorsal area was planned as part of a subsequent, planned hospitalization.

Discussion.

The frameworks of certain standards are in principle nice as definitions or ideal ″imaginary boundaries″, but their applicability in real conditions often turns out to be impossible or in practice in this case we are talking about ″absolute inapplicability″.

We should not ignore the fact that the state of ″absolute inapplicability″ is created by someone and again for the benefit of someone in order to block again ″something″ (as action or nonaction), while at the same time being given the ″green light″ for another kind of action or nonaction? Similarly, to what has just been shared: for 40-60 years now, nitrosamines have been ″tolerated″ in the most commonly used medicines worldwide for the benefit of pharmaceutical companies, and this ″enforced tolerance″ is still ensured by the control authorities [1,10]. The notion sounds absurd but remains real: ″forced regulatory tolerance by necessity″, which in 2018 has also become at least a ″conscious forced regulatory necessity for tolerance of carcinogens in the most commonly prescribed medicines worldwide″.

Or is it actually both units (of producers and regulators) that 1) on the one hand regulate the creation of the cancer pandemic, and 2) manage and sustain its existence globally? Or to put it even more clearly in the distant past- ″the production and regulatory units of the planet″ follow the wise postulate: ″Divide and conquer″.

Both units seem to follow history and learn from it quickly/ easily, which could also be described as commendable: ″You create a problem that only you can solve, and in the process of creating and solving it: you can only make a profit!″ Unfortunately, the thirst for profit often leads to a loss of control, followed by irreparable, catastrophic damage to public health. And it is called: (skin) cancer pandemic.

Following the identification and official initial condemnation in 2018 of the ″so long denied carcinogen contamination″ globally, the processes of its ″forced legalization″ or allowing permissive availability in the form of so-called daily acceptable intake dosis have been launched. Unfortunately, this undoubtedly ″gallant gesture″ by regulators to manufacturers is practically unworkable for polymorbid patients or those with multimedication. The reason for this impracticability is further supported by the lack of a general calculation capability within the framework of polycontamination, namely: 1) neither clinicians are able to calculate these concentrations daily and repeatedly (in time and in engagement related to each patient), 2) nor are these real concentrations labelled in the package leaflets of the respective drugs (as promised) to allow, at least in theory, the calculation of risk.

We are not even referring here to the additional inhalant component as an aggravating factor within smoking (active/ passive) [11,12], nor to the dietary component within heterogeneous/difficult to control, individual diets (3-7)(diets - one, perhaps - again a regulatory problem?) But the problems are not only in these units.

One should also take into account the fact that personalized medicine remains unrealistic for more than 95% of the population on Earth precisely because of modern trends or common perceptions, because of the killer rates of globalization, or because often 1) you have to become a ″doctor at any cost″ because it is fashionable or otherwise put: you have to respect the tradition in the family regardless of genetic burden (which however is not in favour of scientometric parameters, for example)

″ In practice, the problem also appears to be the severe universal morbidity that we ourselves are in fact creating by allowing the spread and intake of carcinogens within the framework of multimedication and polycontamination with nitrosamines ? And when that reality is justified or based on the quick and prioritized interests of only certain circles, it is severe. A reality analogous to that of nitrosamines in the most commonly distributed drugs worldwide and unfortunately: a ″coercive reality″ again.

Ideal parameters and definitions exist in practice in textbooks, guidelines, galactic parallel reality handbooks, etc., and it should be noted that they do not always follow the dynamics of the evolution of the human mind, of environmental events and adaptation processes- whether in the form of behavioral reactions (avoidance of a threat/passive) or : active action to identify and quickly, permanently eliminate a potential danger. They follow not infrequently someone's interests.

A number of questions remain open: where and why has the relevance and power of prospective follow-up in terms of proving causality been lost in the analysis of significant clinical observations worldwide? Why, 5 years after the first nitrosamines were formally available in valsartan in 2018, are such follow-up studies lacking? Why are batches of different classes of drugs being quietly withdrawn globally even though they pose no threat to patient health (according to official bodies)? Since when do regulatory authorities actually know about the presence of nitrosamines in medicines?

Why are the issues concerning the problems of polymedication and polycontamination with nitrosamines not clearly and precisely formulated?

In effect, we are witnessing the loss of social responsibility/ identity in medicine in an effort to follow the modern priorities of the environment: modern drugs, modern lectures, modern hospitals, modern advertisements, modern loss of identity, modern opinions of the powerful of the day. Subsequently, a quieter life can probably be led. In practice, however- conformity is not obligatory? And social, moral, and scientific responsibility are or can be the product of the individuality of each of us [13]?

And this is what should be defined as (in)valuable contributions.

Analogous to the contribution concerning equivalent to completely overlapping patterns/ examples of clinical manifestations of skin tumors after intake of heterogeneous type of drugs contaminated with carcinogens/mutagens or so-called nitrosamines [1]. It is the ingestion of nitrosamine-contaminated drugs with radically different mechanisms of action and the consequent uniform development of skin neoplasms that underlies the definition of the term: skin cancer nitrosogenesis.

An observation that definitely sets a new logical beginning in terms of the analysis and interpretation of medical information. And an observation that has now also become a phenomenon conditioning a radically different interpretation of skin cancer pathogenesis [9].

The first case we presented was of a patient who took bisoprolol in combination with amlodipine/valsartan for 10 years and subsequently developed keratoacanthoma, multiple actinic keratoses of the scalp and two dysplastic nevi in the dorsal area. The time of availability for keratoacanthoma was a few months whereas that for nevi was a few years. Because of the rapid development of keratoacanthoma and the history of painful sunburns in the past, the association with medication intake could be sporadic but should not be ignored as a model for analysis.

Data on the development of epithelial tumors in association with dysplastic nevi after bisoprolol, amlodipine, and valsartan intake are available in the medical literature even in young patients without a history of painful sunburns [14].

Similarly, data on the development of basal cell carcinoma and dysplastic nevi after taking valsartan in combination with hydrochlorothiazide potentially contaminated with nitrosamines are also available [15].

The combination of the occurrence of multiple basal cell carcinomas and dysplastic nevi after taking enalapril and perindopril has also been described [16].

Recently published data again hint at the risk of developing keratinocytic tumours after taking potentially contaminated drugs from the group of calcium antagonists: amlodipine and felodipine: felodipine in combination with hydrochlorothiazide/ development of basal cell carcinoma; amlodipine in combination with bisoprolol/ simultaneous development of squamous cell and basal cell carcinoma of the face [1].

Multiple nevi in younger patients in areas not exposed to intense solar radiation could also occur after taking valsartan in combination with amlodipine, potentially contaminated with nitrosamines [17].

The small differences in the type of manifestation of epithelial tumors could also be theoretically explained to some extent by the heterogeneous type/concentration of the respective nitrosamine and/or the indolent predisposition of the affected patient.

In fact, in the patient described, there is evidence or initial signals of a possible association between the occurrence of potential melanoma precursors in the face of dysplastic moles in combination with an epithelial skin tumor in the scalp area: keratoacanthoma. The overlap of the corresponding clinical pattern after intake of other, potentially contaminating but fundamentally different in mechanism of action drugs (bisoprolol, amlodipine, valsartan)/ (valsartan and hydrochlorothiazide)/ (enalapril and perindopril)/ (felodipine and hydrochlorothiazide)/ (amlodipine/ bisoprolol)/ (valsartan and amlodipine) , is indicative of just such a possibility.

There are also much more serious combined variants concerning the clinical manifestation/appearance of melanoma and basal cell carcinoma after taking both a potentially nitrosamine-contaminated ACE inhibitor-perindopril [18].

The second case we described concerns the simultaneous development of multiple basal cell carcinomas in a Bulgarian patient after taking bisoprolol, amlodipine and valsartan. The date of the initial occurrence of one of the tumours (the one in the back region) predates the intake of the drugs, namely: the date of the complaints from 2015/2016 (asymptomatic lesion no larger than the size of a bean) , while the first intake of bisoprolol is dated (according to anamnestic data) only in 2018 (two years later); of amlodipine in 2019 (3 years later); of sacubitril/ valsartan in 2020 (4 years later). In practice- the concurrent intake of the three potentially nitrosamine-contaminated drugs starts in 2020 and it is probably this period that could also be considered hypothetically as the period of exceeding the so-called acceptable daily intake dosis.

The data on the increase in tumour size concerning basal cell carcinoma of the back are from 2021 or one year after the combined intake of the triple combination of potentially contaminated drugs (bisoprolol, amlodipine, valsartan). The tumor in the shoulder area occurred in 2019 or immediately after the addition of amlodipine to the treatment regimen for arterial hypoertension , increasing in size and becoming symptomatic only in 2021: one year after starting the triple antihypertensive combination of bisoprolol, amlodipine, and valsartan.

The fact that for the empaglifozin taken by the patient (patient 2) over the last 5 months, different methodologies are being developed (currently worldwide) to exclude nitrosamine contamination could be seen as at least worthy of clinicians' attention [19].

Metatypical basal cell carcinomas could also develop after intake of nitrosamine-contaminated enalapril and losartan [20].

The occurrence of a high-risk form of basal cell carcinoma within the telmisartan/hydrochlorothiazide treatment or after the intake of two other potentially/really contaminated classes of antihypertensive drugs has also been described [21].

Multiple epithelial tumors (SCC, metatypical BCC) have also been observed within systemic administration of valsartan in combination with chlorthalidone [22], and both classes of drugs belong to those declared as potentially/actually contaminated (sartans, thiazide/thiazide-like diuretics) [23,24].

The recent international data from a Japanese research team, which linked monomedication with thiazide diuretics (in patients with arterial hypertension) to the development of squamous cell carcinomas of the skin [25], should not be ignored. Another question is whether this is solely due to their photosensitizing action or is nitrosamine contamination the leading cause?

Similar to the above data, Canadian researchers have found an association between the long-term intake of a certain thiazide diuretic and the development of 1) on the one hand- melanomas,

but also 2) the heterogeneous forms of keratinocytic cancer [26].

A German study from 2022 linked the development of keratinocytic cancers to the intake of hydrochlorothiazide and ACE inhibitors [27].

The third patient described is indicative precisely of the issues concerning polycontamination within multimorbidity and polymedication. Within the last 5 months, the patient noticed the appearance of a tumor formation in the nasal area, verified histologically postoperatively as a basal cell carcinoma. The patient's systemic antihypertensive therapy for the past years includes : 1) short-term several months of perindopril and amlodipine- 2023/ for about 6 months; 2) enalapril maleate for about 5 years/ for the period 2015/2022; 3) losartan potassium/ hydrochlorothiazide/ for the period 2020-2022; 4) Metformin from 2012 to date/ 2023; 5) Paroxetine/ SSRIs/ selective serotonin reuptake inhibitors: One per day for 3 years/ from 2020; 6) Flupentixol / Melitracen as the withdrawal period is from 3 years and lasts until now/ see case 3.

Intrapretation of the data is extremely difficult precisely because of the concomitant but also partly episodic intake of a total of 5 medications that are reported to belong to the groups of potentially/really nitrosamine contaminated: 1) ACE inhibitors, 2) sartans, 3) Thiazide diuretics, 4) metformin, 5) / SSRIs/ selective serotonin reuptake inhibitors and 6) tricyclic antidepressants.

The development of basal cell carcinomas after potentially contaminated drugs has been described after perindopril/ enalapril administration [16,18] as well as after losartan therapy [20]. The nitrosamines in metformin have also been described as possible triggers for the development of basal cell carcinomas [28].

Similarly, in the patient we presented in number 3 (who was taking losartan) , the intake of a certain sartan (in this case-telmisartan) in combination with amlodipine could also be defined as risky in terms of the development of giant basal cell carcinoma because of possible contamination with nitrosamines [29,30].

The use of tricyclic antidepressants such as amitriptyline, for example, could also be problematic precisely because of its contamination with nitrosamines [31,32]. Melitracen, taken by the patient, also belongs to this group of medications, but there is currently no literature/regulatory data on its potential contamination with nitrosamines. Precisely because of this fact, the medication concerned should be screened for the presence of nitrosamines, similarly to amitriptyline.

The patient is indicative precisely with regard to the fact that she is also the first patient in the world literature to develop keratinocytic cancer after taking Melitracen/ a tricyclic antidepressant in the context of polymedication and possible polycontamination (see also the other potentially contaminated drugs taken by the patient).

The last two concepts (polymedication/polycontamination) make accurate determination of the pathogenetic significance of any potentially contaminated medication (taken by patient 3) extremely difficult. But this significance remains logical and entirely possible as a thesis.

The concomitant administration of Paroxetine/ SSRIs/ selective serotonin reuptake inhibitor by the same patient further supports the thesis regarding the nitrosogenesis of skin cancer due to the fact that this group of medications has also been described as being affected by nitrosamine contamination [33].

In practice, the patient was taking a total of 6 potentially nitrosamine-contaminated drugs, and the contribution of each individual group to the development of skin cancer remains unclear. The reason for this is that the medication leaflet lacks data regarding the concentration of the respective nitrosamine, as well as data regarding its absence or availability in general.

The fourth patient presented with histopathological evidence of 2 skin tumours after surgical excisions: a basal cell carcinoma involving the right nostril and a trichoadenoma in the forehead, as well as a dysplastic nevus in the right temple. The tumors were resected in sano.

The duration of the complaints concerning the lesion in the nasal area was 6 years (2017) and the tumor in the forehead area was 2 years (2021). The duration of the nevus is unclear according to history, but it became noticeable to the patient about 2 years ago. The intake of medications officially reported to belong to the group of potentially contaminated.

Biosprolol fumarate: for a period of 10 years, 2) venlafaxine: for a period of 6 years, and 3) arihaban: for a period of 2 to 3 years/ see patient history 4. Apparent progression of tumours (according to anamnestic data) was observed within the combined intake of the respective drugs during the last 2 years.

And while the development of keratinocytic cancers after intake of potentially nitrosamine-contaminated beta blockers (bisoprolol/ metoprolol) is no longer or recently a novelty (1), the data for the other two classes of drugs venlafaxine/SNRIs/ serotonin and noradrenaline reuptake inhibitors, and apixaban/ anticoagulants, are also not a big surprise.

The reason why is that 1) it is batches of tricyclic antidepressants and 2) SSRIs/ selective serotonin reuptake inhibitors that have been pulled from the market due to nitrosamine contamination [31-33]. And this is what makes venlafaxine contamination entirely possible as well?

Apixaban is an anticoagulant that blocks factor Xa [34].

Based on the fact that batches of another anticoagulant (Dabigatran) have recently been withdrawn from the drug market [35,36], contamination testing of apixaban in the near future seems more than feasible.

Conclusions.

1. The Nitrosogenesis of skin cancer is a concept that has become increasingly important over time.

Contrary to the recently accepted worldwide perceptions that define patient polymorbidity as a key or risk factor in terms of carcinogenesis (carcinogenesis not only concerning skin cancer), but the following could also be shared on the basis of current clinical observations: Polymedication in multimorbid patients and the current polycontamination with nitrosamines (affecting almost all the most commonly taken classes of drugs) could be the real cause of the ″skin cancers pandemic″. The rough calculation for patients taking this medication is of

apocalyptic proportions and the data on it remains currently hidden from end consumers and the most of the clinicians.

2. The number of medications actually contaminated with nitrosamines includes (according to official data) the contamination of ACE inhibitors , Beta Blockers and Thiazide diuretics, with batches of these medications being quietly withdrawn from the commercial market. Parallel or combined intake of these groups of drugs (even when the nitrosamines they contain are within acceptable limits) is also likely to be associated with exceeding the daily acceptable dose of a particular carcinogen or group of carcinogens. These processes are not yet defined and cannot be monitored at the moment.

3. In the first two patients we described who developed keratinocytic tumors and melanoma precursors after combined administration of a beta blocker and sartan, the presence of amlodipine in the patients' ″medication menu″ is again remarkable. Future investigations in this regard should be prioritized and publicized, as these data have been confirmed in observational studies of other groups of patients taking calcium channel antagonists for the treatment of arterial hypertension (1). The different types of skin cancers after intake of potentially nitrosamine-contaminated drugs could be explained by the heterogeneous type of nitrosamines found within the contamination.

4. Combined or stepwise administration of groups of drugs declared potentially contaminated (perindopril, enalapril, losartan, metformin/patient 3) could again be considered as a key element within the carcinogenesis/nitrosogenesis of skin cancer. For the first time in the world literature, the role of potential contamination in the context of nitrosogenesis is also discussed, concerning the concomitant use of two completely new drug groups (within the framework of polymedication and polycontamination) : Paroxetine/ SSRIs and Melitracen/ tricyclic antidepressant. Future investigations against the previously mentioned drugs could clarify their possible pathogenetic role. It should be borne in mind that both groups of drugs have been declared as actually contaminated by regulatory authorities and batches of them have been withdrawn from the market in the recent past.

5. The current work is also confirmatory (and second in the world literature) regarding the role of the potentially nitrosamine-contaminated metformin in relation to the occurrence of basal cell carcinomas.

6. The contributions and the innovative, to some extent preventive message (of the data presented within our clinical observations) also concern the necessity of screening (for possible nitrosamine contamination) of two completely new , previously unannounced classes of drugs: 1) Venlafaxine/ SNRIs, a serotonin and noradrenaline reuptake inhibitor and 2) the anticoagulant apixaban , a highly selective direct factor Xa inhibitor.

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