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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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NITROSAMINES IN COMMONLY PRESCRIBED ANTIHYPERTENSIVES AND THE (UN) CONTROLLED DRUG-INDUCED SKIN CANCER: SIMULTANEOUS DEVELOPMENT OF CUTANEOUS MELANOMA AND MULTIPLE BCC AFTER CONCOMITANT ADMINISTRATION OF BISOPROLOL AND FUROSEMIDE

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Abstract.

The era of nitrosogenesis is the era that is conditioned by the permanent and prolonged intake of carcinogens/mutagens, also known as nitrosamines/NDSRIs in the context of polymedication/polycontamination in polymorbid patients.

Until recently, the favoured and universally accepted thesis by the scientific community that polymorbidity determines the risk of developing cancer has been shown to be weakly substantiated and superseded by the more modern notion that: it is the polycontamination with carcinogens in the context of concomitant medication/ polymorbidity that determines to a large extent the risk of developing heterogeneous cancers, including skin cancer: keratinocytic and melanocytic.

The FDA is the organization that first pulled back the curtain on the backstage back in 2018 on this topic. It was not until 2023 that the FDA again catalogued over 250 drugs that are affected by contamination with carcinogens/mutagens/NDSRIs having varying carcinogenic potencies graded between 1 to 5.

The expectations of clinicians and patients globally at the moment remain hopeful that the diplomatic recommendations of regulators will soon be replaced by more restrictive regimes and sanctions. The reason for the need to clarify this issue quickly is due to the following circumstances: 1) The reassuring calls and analyses of the regulators that the minimum intake of carcinogens (nitrosamines or intake within reference values) , could not become a threat to the health of patients even after 70 years of intake, appear to be rather inconsistent; 2) Lack of any official data on any drug batch that has at least been declared by the FDA/EMA (if declared at all) as potentially contaminated; 3) Another not insignificant reason is that a number of scientific publications are indicative of exactly the opposite: short-term concomitant intake of polycontaminated drugs leads to short-term cancer development while shortening cumulative survival and quality of life for those affected.

Only the transparency of the results of checks carried out on the presence of carcinogens in drug batches can guarantee peace of mind, and this in turn can be guaranteed by the regulatory authorities.

4) In parallel, the number of clinical data indicating an association between the intake of potentially nitrosamine-contaminated drugs (mainly for high blood pressure, but not only) and - in particular - keratinocytic and/or melanocytic skin cancer is growing avalanche-like.

The dramatic increase in skin cancer in general/ worldwide is in absolute contradiction to the continuous explanations that the most important factor in the generation of skin cancer is ultraviolet light and sunburn: the incidence of skin cancer is increasing despite the widespread intensive use of sunscreen protection creams, the lack of any sun exposure in certain groups of patients, and its occurrence in areas not exposed to solar radiation. It follows only that solar radiation is not the only and perhaps not the most important factor determining the occurrence and progression of skin cancer.

We report another concomitant intake of potentially nitrosamine contaminated blood pressure medications: bisoprolol and furosemide, taken over a period of 7 years that resulted in the concurrent occurrence of a medium-thickness cutaneous melanoma and 2 basal cell carcinomas.

Successful surgical treatment of the tumors was performed, and the role of concurrent administration of ″hypothetical″ class 4 carcinogens within the framework of polymedication, polycontamination, and polymorbidity is discussed.

Key words. Furosemide, bisoprolol, nitrosamines, BCC, melanoma, polimedication, skin cancer, photosensitivity, DNA damage.

Introduction.

According to some of the most advanced views on the pathogenesis of skin cancer, the relationship between the occurrence of epithelial skin tumors and the intake of a certain class of drugs could also be determined by the presence of so-called nitrosamines [1]. The presence of these ingredients as possible contaminants has been confirmed by the FDA and their permissible availability has been defined by strict recommendations to manufacturers [2]. Monomedication or polymedication involving heterogeneous types of preparations (which are listed by the FDA as potentially/ hypothetically contaminated) has been defined by several authors as problematic, as it could be associated with the generation not only of skin cancer but also of cancer in general [3,4].

We report a polymorbid patient who developed 2 epithelial tumors and one superficial spreading melanoma during his relatively short-term multimedication intake. The potential relationship of possible contamination in the context of skin cancer nitrosogenesis is discussed [5].

Case report.

An 85-year-old patient presents with a history of complaints of approximately 2-3 years in the form of right shoulder discomfort and a problem involving the lower lid of the left eye (Figures 1a,1b). The reason for the examination was to clarify the dignity of the lesions in these areas and determine further diagnostic and therapeutic algorithms. The patient's comorbidities include arterial hypertension, chronic congestive heart failure, high grade aortic, mitral, and tricuspid insufficiency, atrial fibrillation, pulmonary hypertension, cholelithiasis, hiatal hernia, gastritis, iron deficiency anemia and idiopathic thrombocytopenia. Accompanying medication includes:

bisoprolol (5 mg x 1/morning + 1/evening), furosemide (40 mg x 1/morning + 1/evening) , spironolactone (25 mg x 1/morning + 1/evening, apixaban 2,5 mg / twice daily, a combined tablet containing magnesium DL-aspartate tetrahydrate 175 mg and potassium DL-aspartate hemihydrate 166 mg (175 mg + 166 mg x 2/morning + 2 + 2/evening) pantoprazole (40 mg x 1 daily. Idiopathic thrombocytopenia was treated with good results with Eltrombopag (25 mg x 1/day). The medication with bisoprolol, furosemide and spironolactone were reported by the patient as ongoing in the last 7 years.

The dermatological examination revealed the presence of three primary cutaneous tumors in the following regions – regio infraorbital is sinistra, regio presternalis and regio scapularis dextra. The first lesion, found in regio infraorbitalis sinistra, in close proximity to the lower eyelid, was exophytic with a centrally located erosive surface. The surface was covered with hemorrhagic crusts. The lesion had a slightly raised peripheral edge, suspected of nodular BCC (Figure 1a). The second lesion, found in regio presternalis, was pigmented and had irregular shape suspected clinically and dermoscopically for cutaneous melanoma (Figure 1c).

The third lesion was found in regio scapularis dextra and had a diameter of approximately 6-8 cm. It was an exophytic oval tumorous formation, its surface being ulcerative and heavily bleeding, suspicious for epithelial tumour again (Figure 1b). According to the patient, all of the lesions appeared together and started growing simultaneously 2-3 years ago.

Surgical removal of the three formations was planned under local anaesthesia within one surgical session.

The lesion located in regio presternalis, suspected clinically and dermoscopically for cutaneous melanoma, was removed by elliptical excision under local anesthesia (Figures 2a-2c). The surgical safety margin was 0.5 cm in all directions (Figure 2a). Single interrupted stitches were used to close the surgical defect left by the excision (Figure 2c). The histology was indicative for superficial spreading melanoma, Breslow 2mm, Clark III, clear resection lines, stage IB (T2aN0M0). Reexcision was planned with an additional field of surgical safety in combination with detection and removal of a draining lymph node regarding the AJCC/EJC recommendations for surgical treatment of cutaneous melanoma. Due to the fact that the patient was classified as high-risk patient, it was discussed to limit the surgical intervention

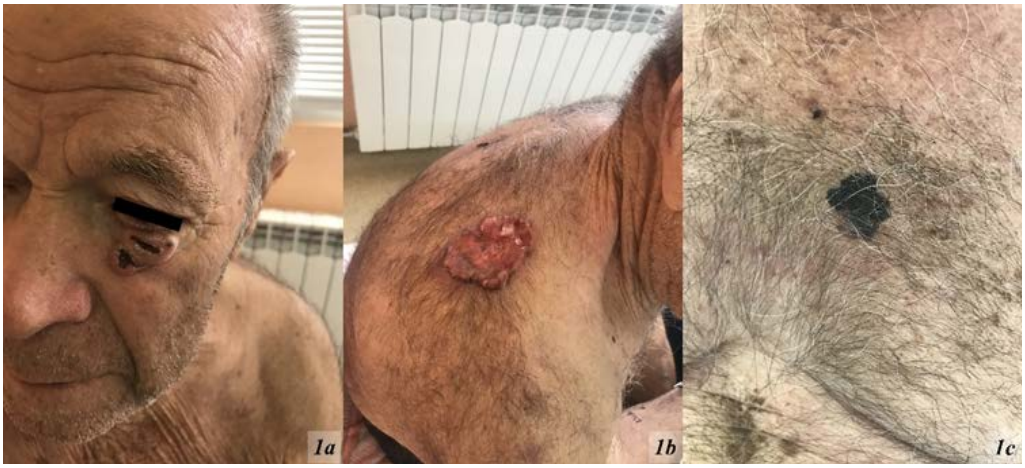

Figure 1. 1a. *Nodular cutaneous tumour localized under left lower eyelid.*
1b. *Plaque-like growing tumour formation in the area of the right scapula, clinically suspicious for keratinocytic cancer.*
1c. *Presternally localized pigment lesion, clinically and dermatoscopically suspicious for cutaneous melanoma.*

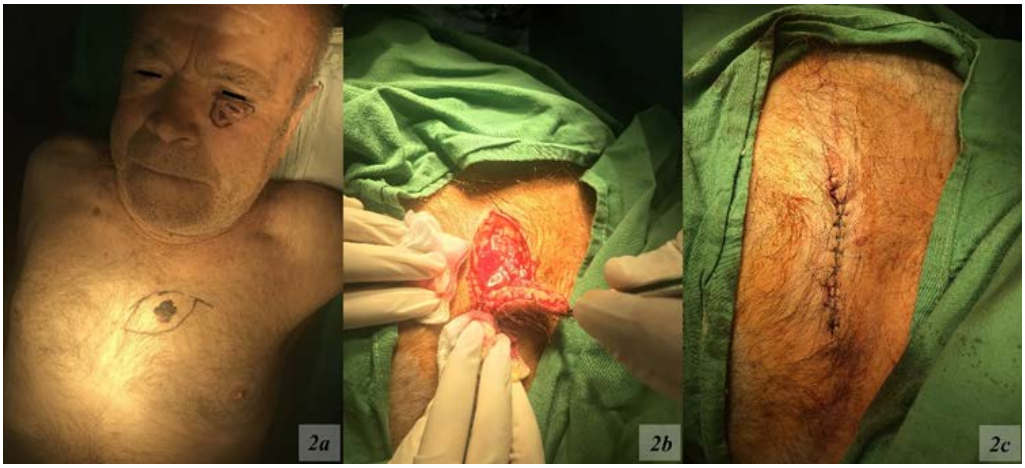

Figure 2. 2a. *Highlighting resection margins prior to surgical removal of cutaneous melanoma.*
2b. *Surgical removal of cutaneous melanoma in the form of an elliptical surgical excision.*
2c. *Immediate clinical finding after closure of the defect with single skin sutures.*

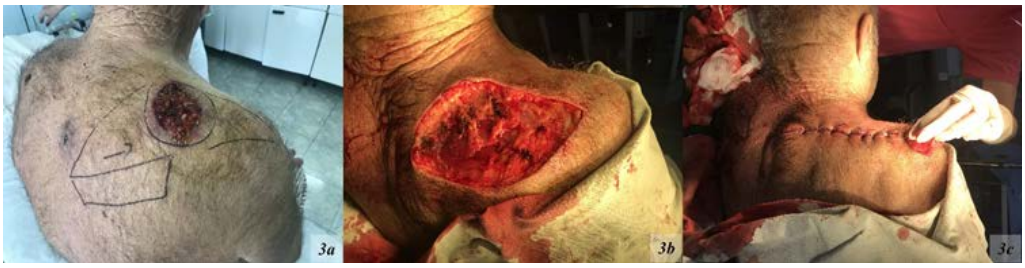

Figure 3. 3a. *Marking of resection margins prior to surgical removal of epithelial tumor in the area of the right scapula.*
*3**b.** Intraoperative finding after stopping the bleeding and before closing the defect.*
3c. *Postoperative finding immediately after closure of the defect.*

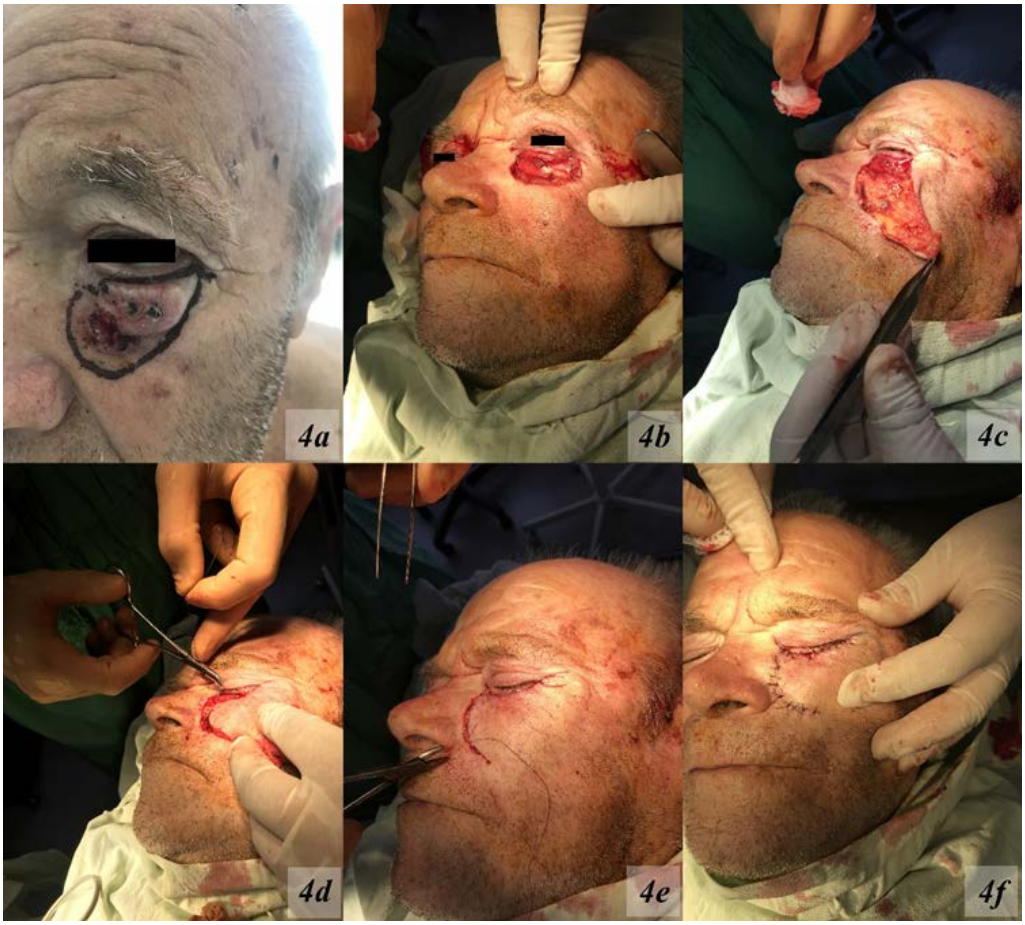

Figure 4. 4a. *A cutaneous tumor localized under the left lower eyelid. Marking of resection fields.*
4b. *Condition after surgical removal of the tumor. Intraoperative finding.*
4c. *Performing a melolabial advancement flap to cover the resulting defect.*
4d. *Careful adaptation of the wound edges by means ofsubcutaneous sutures in order to achieve an optimal aesthetic result.*
4e. *Placement of single skin sutures and adaptation of wound edges.*
4f. *Postoperative findings after a melolabial plastic.*

within the re-excision only and to register him for follow-up at the regional cancer hospital.

The lesion localized in regio scapularis dextra, suspected for spinocellular carcinoma, was removed by extensive elliptical excision under local anesthesia and the diagnosis of BCC was made again, T2N0M0, clear resection lines (Figures 3a-3c).

The tumor formation in the area of regio infraorbitalis sinistra which was suspected of basal cell carcinoma, was surgically removed with small surgical margin and the defect was closed by melolabial advancement flap (Figures 4a-4f).The histology was indicative of solid BCC, stage 2 (T2N0M0), clear resection lines. The patient had a fast and full postoperative recovery.

Discussion.

The potential association between beta blocker intake and the development of melanomas is not new and has been known for years [6].

However, other international follow-up studies do not confirm the existence of such a relationship between beta blocker intake and melanoma development and progression [7].

The potential relationship between the intake of antihypertensive drugs and the development of melanoma, as well as other types of potential skin tumors, has been a subject of discussion for years, and has not yet found a definitive solution [8].

It is believed that within systemic antihypertensive medication, subsequent photosensitization and sunburn could lead to changes in DNA (in predisposed individuals), and it is this that is capable of generating the malignant cell clone giving rise to skin cancer in general [8].

Articles in the literature have also described the potential `positive role' of beta blockers on pre-existing melanoma cells [9].

Although even under experimental conditions beta blockers show antiproliferative or antitumor effects [10], its clinical significance/relevance at present , remains more than controversial [1,5].

This controversy or divergence of opinion is explained by the following few not unimportant facts, which should be given more detailed attention:

1) In patients with melanomas, beta blockers could have an antitumor effect (but in already present thick melanomas) and thus prevent probably recurrences [11] (this effect is due to the influence of the active, pure substance), and

2) Nitrosamine-contaminated beta blockers could lead to the generation of all forms of skin cancer within nitrosogenesis - melanocytic and keratinocytic as well as melanomas [1,5].

Hence the following interesting question to colleagues formalizing the positive effects of beta blockers to pre-existing melanoma cells in patients they have observed and published [9,11].

″Were these melanoma patients taking beta blockers before the melanomas occurred? And for what period? Was there any evidence of concomitant medication that preceded tumor onset or that, according to the 2023 FDA list, was declared potentially contaminated with nitrosamines? ″

Although the answers to these questions are unambiguous and indicative of the leading role of nitrosogenesis in the development of skin cancer, prestigious peer-reviewed journals do not allow these questions to even be formally asked of them. And this is more than indicative of serious flaws in the analysis of the data of the relevant scientific works, as well as their one-sided interpretation and lack of thoroughness. In addition to what has been shared, not even a new thesis or point of view is allowed.

In practice, the individual ingredients contained in the tablet itself have a different mechanism of action. One (the nitroso component) - generates cancer [1,5], and the second (the active ingredient / beta blocker) - slows its metastasis for a period of time, however, when the cancer has already occurred and moreover only in certain cases [11].

The problem is that the nitroso component is not labelled on the packaging but is ubiquitously or sporadically distributed together with the active substance. In practice, consumers have no choice.

It is also problematic that the number of keratinocytic and melanocytic cancers after receiving antihypertensive polymedication within the framework of polymorbidity and nitrosamine contamination is skyrocketing and includes a heterogeneous class of antihypertensive medications in addition to beta blockers [12-14].

Bisoprolol, taken by our patient for a period of 7 years, is also included in the FDA list of potentially nitrosamine-contaminated drugs [2]. The carcinogenic potency of the drug was determined to be class 4 , and the reference values for potential intake of this preparation amount to 1500 ng/day [2].

Photosensitivity, and the potential side effects that follow (such as DNA mutations), are also associated with the use of certain betablockers [15]. The combination of 1) photosensitivity and 2) daily intake of potential carcinogens/mutagens, in the context of beta blocker therapy, certainly has at least a synergistic effect with respect to the skin cancer development [1,5,15].

The second parallel medication taken by the patient is furosemide. It is ″problematic again″ because of two circumstances: 1) The photosensitizing effect of furosemide associates it (according to international data) with a significant risk of developing keratinocyte cancer (basal cell carcinomas and squamous cell carcinomas) -over 20% with long-term use [16], and on the other hand: 2) FDA classifies in April 2023 the drug furosemide, similarly to bisoprolol, also to the potentially nitrosamine/NDSRIs contaminated class 4 carcinogens [2].

Parallel intake of these two drugs (bisoprolol and furosemide) could be associated in at least 2 different lines with the generation of skin cancer/ cutaneous melanoma and keratinocytic cancer/ : 1) the presence of a nitroso component that is possibly/ probably many times higher than the permissible daily intakes of carcinogens defined in 2023 by the FDA [1,2,5], and 2) mutually potentiating photosensitivity within the polymedication with a beta blocker and a loop diuretic [15].

The lack of a history of painful sunburns in the patient, as well as the negative family history of skin cancer, favor and emphasize once again the thesis of a possible key role of nitrosogenesis of melanocytic and keratinocytic skin cancers, similarly in synchrony with other data [1,5,12,13,17].

The nitrosogenesis of skin cancer is likely the key to unraveling its pathogenesis [1,5].

A number of facts concerning the processes of contamination could be considered from another angle of refraction of thought and reasoning.

A recently published study by the Turkish Collective contains seemingly encouraging data, namely that: none of the ARBs/ sartans tested for the presence of nitrosamines showed a positive reaction or reaction for the presence of carcinogens/mutagens/ nitrosamines [18]. In practice, this is indicative of the following: 1) contamination is not ubiquitous, 2) contamination may be limited to completely absent, 3) certain geographic regions may remain unaffected- contamination may be geographically determined or ″completely controlled″, 4) one can speculate from point 3 and conclude that certain geographic regions could also be ″controlled affected″ within a certain time range, and that: 4) Contamination and its detection is an alarming sign of a serious health risk.

The number one priority of regional control bodies in every geographical region and every country is - to keep it missing and this is quite possible as has been demonstrated in our neighbouring country [18].

As long as contamination can be cleared in certain areas in a controlled manner, there is nothing to prevent it from being caused in a ″controlled manner″. It is logical to think in the direction that the absence and presence of carcinogens in medicines could be controlled.

The suspicion of controlled, time-limited contamination of certain productions in certain geographic regions is also one of the most logical explanations for the conflicting scientific data available in the world literature concerning the intake of a certain drug and the development of a certain form of cancer: in this case bisoprolol and furosemide.

The sporadic contamination with nitrosamines and the complete lack of such contamination in certain geographical regions are indicative of the following: sporadic contamination may or may not be controlled.

The priorities of the various health systems around the world, regardless of their location and structure, should strictly follow the idea of the system in which they operate: and this comes from its very name - health care: protecting the health of others. And in this case, this could only be ensured by permanent regulatory regional control of each batch of medicines declared or even suspected to be contaminated with nitrosamines/NDSRIs. This remains the only key to solving the problem of sporadic or controlled nitrosamine contamination worldwide: detection and elimination followed by sanctions, not recommendations. Because concepts such as ″hypothetical carcinogens″ and ″eventual/ hypothetical availability″ do not exist , analogous to the reality of the 21st century- ″the age of forced tolerance of carcinogens/mutagens/nitrosamines in medicines due to lack of alternative at the moment″. The FDA definitions of 2023 sound unrealistic: ″reference doses for hypothetical carcinogens within the limits of daily intake.″ There are no hypothetical carcinogens and no reference limits for such - this is the absurd reality that surrounds us and forces us to close our eyes to concepts such as ″Nitrosogenesis″ and ″Controlled cancer″. These concepts are part of the authentic reality, which is not hypothetical.

Because of these unresolved dilemmas, physicians around the world continue to encounter "real carcinomas" after intake of "hypothetical carcinogens", but taken at ″supposedly reference limits″ of which the consumer is not informed.

The polycontamination of multimedication in polymorbid patients, proves and establishes once again : 1) the role of nitrosogenesis of skin cancer, and : 2) that (skin) cancer as a concept and a fact , is in fact a ″controllable concept″ that can be at least minimized, and not spread sporadically or controlled [1,3,5,12,13].

The complete absence of nitrosamine/NDSRIs contamination in certain geographic regions is indicative of just that:

1. Cancer is/ could be a controlled disease!
2. Nitrosamine contaminated drugs are/could be mediators of Cancer!
3. The two irreplaceable, irreversible, and paramount factors for patients are 1) time/life expectancy and 2) health/quality of life. Nitrosogenesis is the factor that negatively affects these processes. The role of regulators is to manage these issues quickly.

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