GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 6 (339) Июнь 2023

ТБИЛИСИ - NEW YORK

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

Monthly Georgia-US joint scientific journal published both in electronic and paper formats of the Agency of Medical Information of the Georgian Association of Business Press. Published since 1994. Distributed in NIS, EU and USA.

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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Содержание:

GEORGIAN MEDICAL NEWS
No 6 (339) 2023

NITROSOGENESIS OF CUTANEOUS MELANOMA: SIMULTANEOUSLY DEVELOPMENT OF PRIMARY CUTANEOUS THICK MELANOMA OF THE BREAST, THIN MELANOMA/ DYSPLASTIC MOLE OF THE BACK DURING PARALLEL INTAKE OF BISOPROLOL, AMLODIPINE AND VALSARTAN/ HCT: NITROSAMINE POLYCONTAMINATION IN THE MULTIMEDICATION AS THE MOST POWERFUL SKIN CANCER TRIGGER

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Abstract.

According to the latest and modern concepts- polymorbidity and polymedication are perceived as one of the most likely triggers for the development and progression of skin cancer (and melanomas in particular). The reason for this should be sought in polycontamination with nitrosamines (in the context of polymorbidity and polymedication of affected patients).

This polycontamination is expanding in scale with each passing day and this in turn allows its detailed (albeit postponed) analysis.

The concept of polycontamination could be related on the one hand to: 1) the patient's medication (number of drugs affected by nitrosamine contamination), but also to: 2) the number of mutagens or so-called contaminants (nitrosamines) contained in a single drug preparation.

Unfortunately, the recently introduced acceptable daily intake dose (ADI) as a concept by the regulatory institutions, does not find its much desired application due to : 1) the lack of precise indication regarding the nitrosamine concentration on the leaflet of each potentially/actually contaminated medicine ; 2) the immediately resulting impossibility to calculate the daily acceptable dose (concentration of mutagens) in each patient (within the framework of polymedication), as well as 3) the ever increasing number/type of those identified in medicines as contaminants,

Thus, in practice, the daily medication intake (of several drugs belonging to the groups of drugs declared as officially contaminated) could have adverse consequences for the health of patients precisely due to the fact that: the concentration of nitrosamines in each of the drugs taken could (not) exceed the acceptable daily intake dose, but the total cumulative intake for the day would (most likely) be - many times higher. At present, however, this calculation turns out to be more of a ″dream″: A delusion or a myth about a personalized medical approach.

On a pragmatic level, it could be concluded that: the establishment of certain stereotypes of clinical behaviour (such as the occurrence of melanomas, for example) after the intake of a heterogeneous class of drugs (which in all likelihood contain relatively similar carcinogens/nitrosamines in terms of composition and concentration), should suggest at least a common pathogenesis.

The article focuses the attention of clinicians on the issues related to the coadministration of potentially nitrosamine-contaminated drugs for high blood pressure (such as Bisoprolol, Amlodipine and Valsartan/Hydrochlorothiazide), while also emphasizing the outcomes that could result from this long-term co-administration: simultaneous appearance of thick melanoma in the left breast area, thin melanoma on the back and dysplastic nevus thoracic on the left.

The Nitrosogenesis of melanoma appears to be a ″new perspective/beam of light″ concerning its pathogenesis, and from a radically different angle of observation.

The confirmatory nature of the clinical picture (multiple melanomas) in the patient we presented could be seen as confirmatory of a number of analogous cases of multiple melanomas occurring after intake of nitrosamine contaminated antihypertensive drugs.

The feasibility of personalized single-stage melanoma surgery, which was applied to the patient presented, is emphasized. The choice of a surgical resection field of 1 cm for thin melanomas with a suspected (clinically/ dermoscopically) tumour thickness of less than 1 mm proved in practice to be an adequate approach, in accordance with the standards of the newly developed innovative guideline for one step surgical removal of cutaneous melanomas (OSMS).

Key words. Nitrosogenesis, melanoma, valsartan, hydrochlorothiazide, bisoprolol, amlodipine, multiple primary melanomas, drug induce melanoma.

Introduction.

The Nitrosogenesis of skin cancer is a concept that concerns all forms of skin cancer: keratinocytic and melanocytic [1,2], but also a number of even rarer forms, such as atypical fibroxanthoma, parapsoriasis plaque, etc [3,4]. Parallel or stepwise manifestation of the aforementioned rare skin tumors/neoplastic skin diseases with others as : 1) atypical fibroxanthoma/ with prostate carcinoma or 2) pre-lymphomas of the large-plaque form of parapsoriasis type/ with bladder carcinoma, have been reported in the context of concurrent prolonged intake of potentially/ actually nitrosamine-contaminated drugs such as irbesartan/ metformin [3] or telmisartan/ metformin [4].

It should be noted also that the intake of telmisartan has been associated with the development of cutaneous melanomas [5,6]. The contamination of polymedication could in practice also be a much more serious problem than previously thought [1].

An analogous situation is the development of melanomas after administration of potentially nitrosamine-contaminated irbesartan [7,8].

The polycontamination of a heterogeneous class of drugs appears to be, in practice, an as yet unsolved problem [1].

The duration and persistence of this problem, (its never-ending clinical repetition/equivalent clinical findings in different patients), directly concerns the nitrosogenesis of skin cancer (but also cancer in general) [1], and is mainly based on several mainstays that have not yet found their definitive solution (but should become priority ones):

1) The lack of any data on nitrosamine contamination in the package inserts of drugs considered to be affected or actually affected by mutagen contamination, and:

2) Polycommunication of polymedication in multimorbid patients (How should it be approached? Individual approach to determine the maximum tolerated dose for the day / within the total drug intake?).

3) The lack of a clear signal from the regulatory authorities: 3.1) to the companies themselves on their obligation to label the actual concentration of mutagens in their products / or definitively stop this production and 3.2) to the patients themselves: not to take medicines that lack indications in the prescription on the packaging about the presence / absence of a certain permissible or elevated presence of certain mutagens / carcinogens: especially in cases where the relevant groups of medicines have been described to date as already contaminated with nitrosamines and batches have been removed from the pharmaceutical market.

We present a patient who, in the context of polymorbidity and polymedication, simultaneously developed 2 melanomas and one dysplastic nevus. Issues of polycontamination and the intake of relevant medications are highlighted, as well as the optimal surgical treatment of melanomas depending on their morphologic characteristics.

The importance of interpreting data based on the equivalent clinical findings/manifestation of the same skin tumor types arising within the context of heterogeneous drug intake is also emphasized, as well as their relationship to the availability of nitrosamines in the drugs underlying this intake. We share the view that the recurrence of these clinical patterns could/should be seen as indicative of a causal relationship between mutagen intake and tumor occurrence.

Case report.

We report a 63-year-old female patient who presented to the outpatient dermatology, venereology, and dermatologic surgery clinic for a new-onset, progressively growing (according to history) lesion in the left breast (Figure 1). In the detailed history subsequently taken, the patient informed of a preexisting lesion in this area, which was no more than half a centimetre in size, homogeneous in colour, regular in shape and asymptomatic overall (achromatic dermal nevus?). The duration of the lesion, according to a rough retrospective calculation (by the patient herself at the time of the anamnesis), was at least 30 years. The changes in the lesion occurred no more than 2 years ago or in 2021 when it progressively changed shape, size, and color.

During the dermatological examination, we found evidence of 1) a pigmented lesion with an asymmetrical shape; unclear differentiation from healthy tissue; non-uniform coloration (ranging from light brown to gray black); diameter, ranging between 1 and 4 cm in different directions; and significant elevation in the centrally located area of the tumor (Figure 1). Dermatoscopic criteria showed a disturbed to completely absent melanocytic network in places; black to light brown areas, regressed white areolae in places. Clinical and dermatoscopic criteria were entirely in favour of the diagnosis of cutaneous melanoma.

In parallel, a second pigmented lesion was noted in the area of the right scapula, suggestive clinically and dermatoscopically of thin melanoma or melanoma in situ (Figure 2).

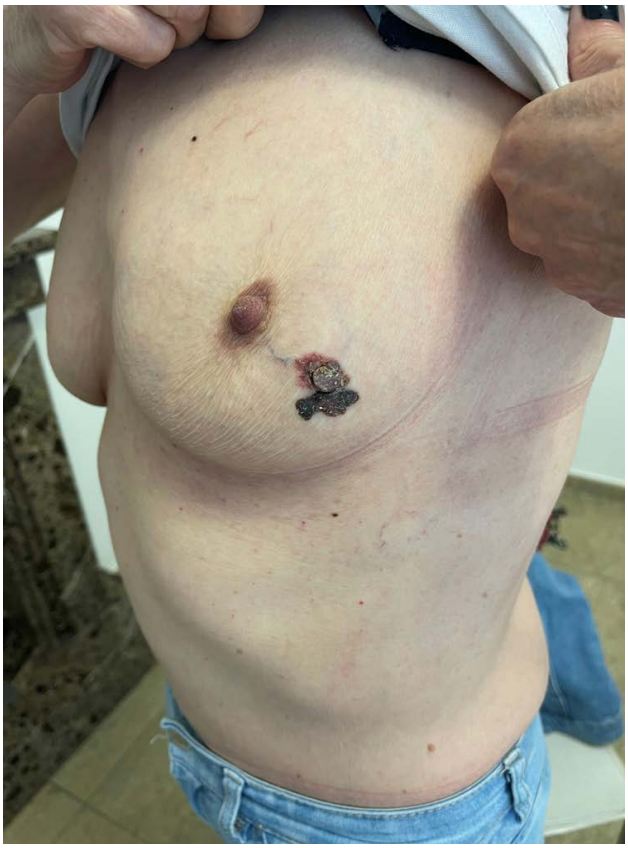

Figure 1. *Patient with suspected cutaneous melanoma on the left breast. Polymorphic clinical and dermatoscopic findings of the lesion: asymmetry, indistinct borders, tricolor, elevation in places, indistinct demarcation from healthy tissue.*

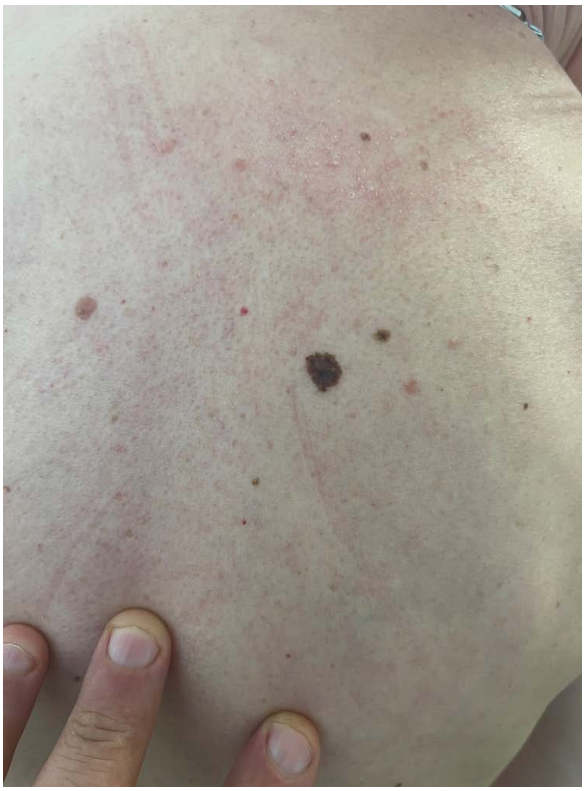

Figure 2. *Pigmented lesion in the dorsal area on the right, clinically and dermatoscopically suspicious for thin cutaneous melanoma.*

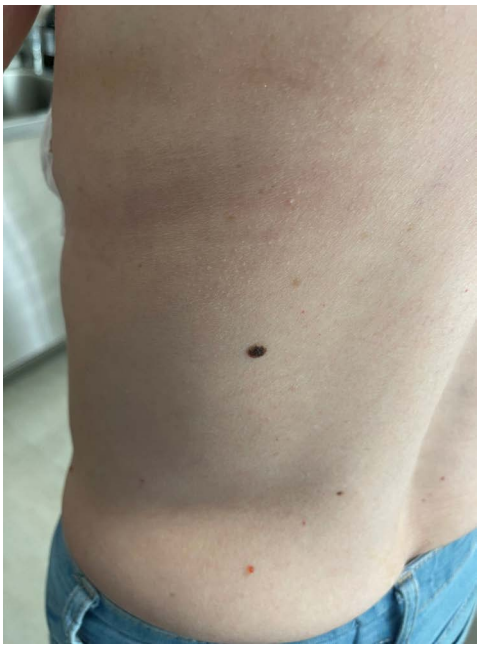

Figure 3. *Pigmented lesion thoracic left, suspicious for dysplastic nevus.*

A third pigmented lesion was also noted lateral thoracically on the left, in the transition zone to the back, which was clinically and dermatoscopically suggestive of dysplastic nevus (Figure 3).

The co-morbidities were known to be ischaemic heart disease, single-vessel coronary artery disease, stable angina/grade three, hypertensive heart disease/grade two, both aortic and tricuspid insufficiency, and adventitial thrombosis of the descending aorta.

The patient's concomitant medications included 1) Bisoprolol fumarate 2, 5 mg twice daily for 2 years; 2) Amlodipine 5 mg once daily for 10 years; 3) Valsartan/ Hydrochlorothiazide 160/12.5 mg once daily for 10 years; 4) Clonidine hydrochloride 0.15 mg as needed; and 5) Rilmenidine 1 mg once daily for 10 years.

Preoperative screening included conducting CT with whole-body contrast as there was no evidence of dissemination of the process. Because of evidence of dissection of the aortic arch and the descending aorta, urgent presentation to a cardiac surgeon was recommended immediately after the 2 excisions were performed under local anesthesia.

Surgical treatment was performed, and excision with a surgical margin of no more than 0.3- 0.5 cm in all directions in the form of an ellipse was applied to the lesion localized in the breast area (Figures 4a,b). The defect was closed using single cutaneous stitches (Figure 4c). The histopathological finding was indicative of the presence of extensive, poorly demarcated, multifocal melanocytic lesion represented by parakeratosis with pigmentary inclusions, proliferation of atypical melanocytes with ascending migration consuming the overlying epidermis, forming heterogeneous atypical melanocytes with pronounced pleomorphism, centrally located nuclei with 1-2 nucleoli, large bright cytoplasms, areas of acantholysis and focal necrosis, pronounced proliferative potential demonstrating more than 5 mitoses per field, some atypical. Scant stromal reaction. No evidence of perineural and lymphovascular invasion. Clean resection lines. Clark 4, Breslow 5.7 mm, nodular malignant melanoma. Stage IIB (pT4aN0M0).

The lesion in the area of the right scapula was removed by one-step melanoma surgery with a surgical margin of safety of 1 cm in all directions to reduce the number of surgical excisions (Figures 5a-5d) (melanocytic lesion present, clinically and dermatoscopically indicative of melanoma in situ /or thin melanoma).

Histopathological data showed: extensive, poorly demarcated melanocytic lesion represented by ortho- and follicular hyperkeratosis, irregular acanthosis, proliferation of pigment-rich melanocytes, elongating and horizontally confluent distal epidermal ridge compartments with foci of ascending migration, marked angiofibroplasia in the papillary dermis with areas of regression and single nests of atypical melanocytes with moderately prominent lymphoplasmocytic stroma. Clear resection lines. Clark 2, Breslow 0.3 mm, Stage IA (T1aN0M0).

The pigmented lesion, suggestive of dysplastic nevus, was scheduled for surgical removal as part of a subsequent hospitalization (Figure 3).

Reexcision of the primary lesion in the breast area by 1.7 cm in all directions, combined with detection and removal of a draining lymph node/ Sentinel lymph node (within the following weeks and after the cardiac findings were clarified) was planned.

Discussion.

The association between cutaneous melanomas and valsartan intake in the context of so-called nitrosogenesis has been known for years and often has fatal consequences for patients [10]. This association is not only based on single literature case studies, but also relies on large-scale retrospective analyses that concern in particular the contamination of valsartan production with NDMA [11]. However, it should not be forgotten that the contaminant is in principle not only NDMA and the contaminated preparation : not only valsartan.

At a sufficiently high dose and duration of therapy, intake of sartans in general (and whether or not they are contaminated with nitrosamines/unstated in the publication) is associated (and according to another research team) with a significant risk of developing all forms of cancer [12]. One logical explanation of these two international follow-ups could be nitrosogenesis and polycontamination within polymedication and polymorbidity. These factors, however, remain unfortunately aside from the statistical evaluations and analyses.

The nitrosamine-melanoma link becomes even more evident if we analyze two new scientific articles concerning the development of multiple cutaneous melanomas after intake of potentially nitrosamine-contaminated preparations containing sartans: [13,14]: 1) The first one describes the development of multiple melanomas after intake of valsartan [13], and the second one: 2) the development of multiple melanomas after similar intake of candesartan [14].

Similarly, melanoma of the skin can also occur after intake of olmesartan and valsartan in combination, and the medication is also considered potentially contaminating with nitrosamines [15].

The contamination of hydrochlorothiazide with nitrosamines is not new [16].

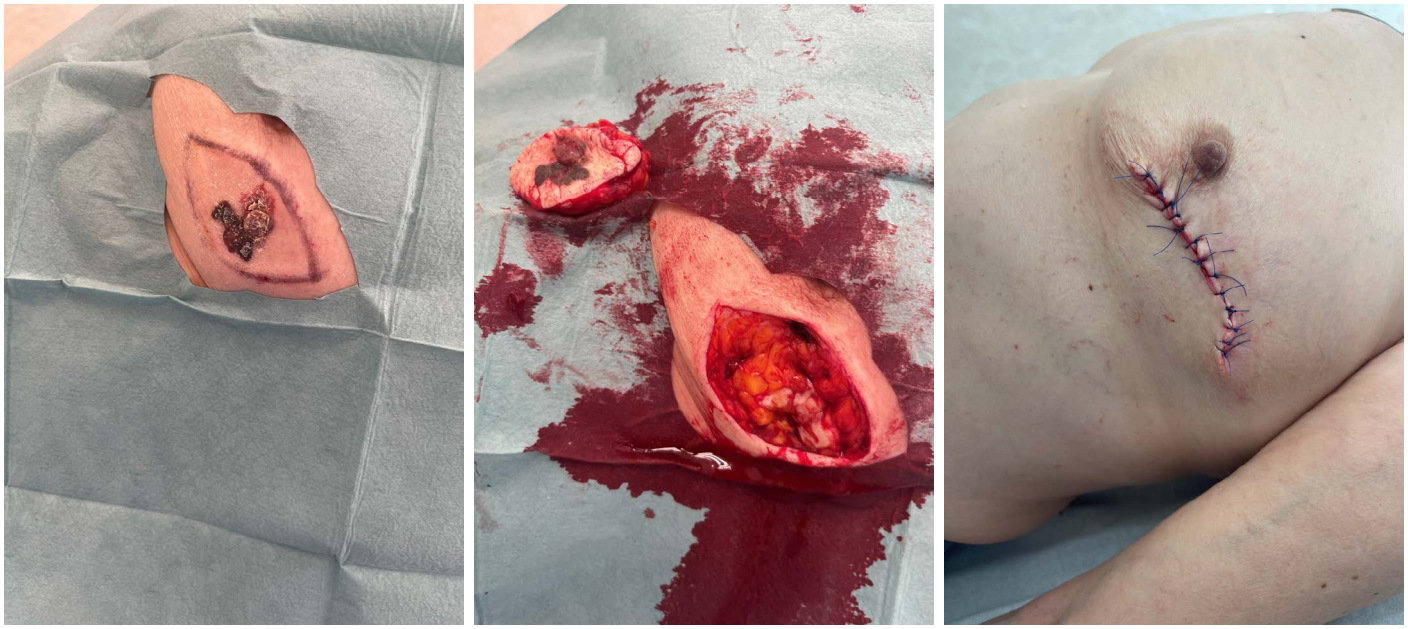

Figure 4. 4a,b: *Surgical removal of cutaneous melanoma with a surgical margin of no more than 0.2 cm in the vertical direction in the form of an ellipse.*
4c: *Postoperative finding after closure of the defect by using single skin stitches.*

Figure 5. 5a: *Selection of a resection margin of 1 cm in all directions in a pigmented lesion clinically suspicious for thin cutaneous melanoma/ OSMS .*
5b/5c: *Performing the resection with a selected surgical margin of 1 cm in all directions and according to the recommendations for an innovative surgical resection margin/ One step melanoma surgery/ OSMS [23,24].*
5d: *Postoperative findings after closure of the defect using single skin sutures.*

The development of melanomas after intake/monomedication of patients with arterial hypertension in the context of hydrochlorothiazide administration is also not new [17].

The occurrence of heterogeneous tumors (cutaneous but also systemic neoplasms) after intake of hydrochlorothiazide and valsartan, for example [18], speaks against the thesis that the procarcinogenic action of the drug is entirely due to its phototoxicity.

This phototoxicity would not be a logical explanation for the development of two other tumors such as Kaposi's sarcoma and colon carcinoma [18].

Similarly, the observation of the development of colon cancer and choroidal melanoma after the intake of hydrochlorothiazide and valsartan, potentially contaminated with nitrosamines, could be similar [19].

The development of melanomas/melanomas in combination with other tumors after taking sartans as monomedication or in combination with hydrochlorothiazide (in the era of polycontamination with nitrosamines/nitrosogenesis) appears to be quite real and possible.

The fact that β-blockers are also a class of drugs that are now formally classified as potentially/actually nitrosamine contaminated should not be overlooked [20,21].

It is for this reason that the occurrence of multiple melanomas after taking beta blockers, (especially also when combined with valsartan/hydrochlorothiazide- as in the patient we presented), should not be surprising to anyone (considering that each of the preparations poses a risk for the development of melanomas even as monomedication).

Melanoma precursors, in the form of dysplastic nevi in

combination with epithelial tumors, have been described in the literature following the administration of beta blockers/ bisoprolol in combination with amlodipine [1].

Any of the drugs taken concomitantly as potentially nitrosamine-contaminated drugs (valsartan, HCT) as monomedication or in combination pose a risk for melanoma development [9-11,17].

Hence, their combined intake could also be a prerequisite for the development of multiple melanomas: a fact repeatedly described in the literature [13,14] and a fact concerning, again, the nitrosogenesis of skin cancer and, in particular, its "melanocytic component" [1].

In practice, polymedication and polycontamination with nitrosamines determine the polymorbidity and development/ progression of multiple skin tumors.

The whole concept is further complicated by the additional intake of the calcium antagonist-amlodipine, recently described and 1) as also potentially contaminated, as well as 2) a constitutive part of the processes of nitrosogenesis [1].

In practice, the polycontamination within the multimedication with 1) Bisoprolol fumarate, 2) Amlodipine 5 mg and 3) Valsartan/ Hydrochlorothiazide) on the occasion of high blood pressure for example, is able to potentiate/generate the emergence of multiple cell clones, in this case: those responsible for melanoma and dysplastic nevi.

This observation has a confirmatory character also with regard to the intake of potentially nitrosamine-contaminated perindopril, and within this intake the development of both melanoma and basal cell carcinoma (but in a stepwise manner) was again observed [22].

It should be noted that it is most likely the variations in the intake of heterogeneous nitrosamines (in terms of type and amount) that are responsible for generating the monomorphic/ polymorphic but also substantially overlapping clinical findings after intake of heterogeneous drug classes [1].

At the very least, these data are indicative of the significance of the pattern concerning an equivalent clinical finding (described repeatedly in the medical literature) occurring in the context of mono- or polymedication of patients who have taken contaminated preparations [1].

This type of finding could be explained as absolutely plausible/ logical/ and quite real within the processes concerning nitrosogenesis determined by polycontamination with mutagens affecting the most commonly administered drugs worldwide [1].

The present publication is also interesting with respect to another topic/dilemma that has repeatedly been the subject of lively discussions worldwide: personalized one-step melanoma surgery/OSMS [23].

Its applicability to certain morphological characteristics of melanomas remains undisputed to this day [24], ″even when coffee is involved″ [25].

The second melanoma described in this publication was treated specifically in the context of OSMS or One Step Melanoma Surgery, thus avoiding one additional surgical intervention for the patient, which is recommended by globally accepted guidelines for the surgical treatment of melanomas according to the postulates of the AJCC/ EJC [26-29].

Conclusions.

1. We present for the first time in the world literature a polymorbid patient who developed 2 cutaneous melanomas and one dysplastic nevus during her polymedication with (1) Bisoprolol, (2) Amlodipine and (3) Valsartan/ Hydrochlorothiazide. The role/significance of potential polycontamination is discussed in the context of nitrosogenesis concerning skin cancer and in particular multiple melanomas of the skin.

2. The publication also emphasizes the possibility of performing personalized one-step melanoma surgery, visually demonstrating the option to achieve optimal outcome in the surgical treatment of cutaneous melanomas.

The surgical safety margin of 1 cm in all directions, in practice, turns out to be a more than ″perfect sparing optimal option″ for thin melanomas / melanoma in situ or dysplastic nevi.

3. The concepts of polymorbidity, multimediation and polycontamination appear to be inextricably linked to each other and are in fact on the way to becoming the leading link concerning the Nitrosogenesis, and thus the carcinogenesis of skin cancer, ...but probably not only...

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