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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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NEIGHBOURING MELANOMAS AND DYSPLASTIC NEVUS DEVELOPING SIMULTANEOUSLY AFTER CANDESARTAN INTAKE: NITROSAMINE CONTAMINATION/ AVAILABILITY AS MAIN CAUSE FOR SKIN CANCER DEVELOPMENT AND PROGRESSION

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Abstract.

Although the problem with nitrosamines and their connection to the generation of skin cancer deepens, it is also thoroughly, carefully, and obligingly neglected. The probable reason for this is in all likelihood the lack of a solution or way out of this situation at the regulatory level. There is almost no sartan (on the European market/ certain countries) after taking which the development of single or multiple melanomas, as well as melanomas in combination with single / multiple keratinocyte tumors, is not observed. But also, skin tumors (again melanomas) in combination with up to two other tumors - simultaneously or subsequently. These cases are immediately reported to the regional regulatory units, but unfortunately to no avail.

Valsartan, irbesartan, olmesartan, and now candesartan is the main ″suspect medications″ for the development of melanomas, regardless of the dilemma: 1) whether the available nitrosamine remains responsible (for melanoma) as a mono/ poly-contaminant (as availability or at a certain dose) or 2) is the generic substance itself also partly to blame?

The literature data on the subject are contradictory, but does not exclude the involvement of any of these units in the generation and progression of melanomas. The lack of official results of possible checks for the presence (of nitrosamines) after the side effect reports were submitted to regulatory bodies further deepened the doubts of the clinicians, supporting the possible pathogenetic role of not only nitrosamines as a key link regarding the development of skin cancer.

In practice, permissive regimes for the availability of carcinogens/mutagens in minimum permissible amounts, have been established ?

It is unclear whether this should be interpreted as a powerlessness of the regulatory authorities in the face of powerful pharmaceutical concerns?

Or is it rather a lull before the start of general regulatory changes and a forthcoming ″shifting of the layers″?

The paradox also arises from the fact that many contaminated batches are quickly, quietly withdrawn from the market, despite being declared harmless or dangerous only for animals.

We report on a patient who developed thin melanoma and neighbouring melanoma in situ after receiving candesartan, treated via one step melanoma surgery within one surgical session with a complete surgical margin of 2 cm. In parallel with the mentioned, a dysplastic nevus was observed clinically and confirmed dermatoscopically in the area of left scapula, for which surgical treatment is planned.

Based on the currently available literature data, a thorough analysis of the role of nitrosamines, as a possible powerful pathogenetic factor for the occurrence and progression of melanomas, was made. The possible role of the generic substance as a cofactor in the carcinogenesis of skin cancer is also discussed.

Key words. Candesartan, drug induced melanoma, wide surgical excision, melanoma in situ, dysplastic nevi.

Introduction.

The clinical manifestation of single or multiple cutaneous melanomas , as well as melanomas in combination with other types of neoplasms such as 1) colon cancer [1], 2) prostate cancer [2], 3) Kaposi's sarcoma/colon cancer [3] (after taking sartans or sartans in combination with hydrochlorothiazide) is not rare [4-7]. The general opinion/thesis is that the nitrosamines (rather than the pure/generic substance) in the high blood pressure drugs are responsible for this clinical manifestation [8-9].

There are also scientific data /in vitro/ that share the potential possibility that the generic substance potentiates metastasis in already available melanoma cells [10,11]. These observations support indirectly the thesis that nitrosamines could lead to the transition of a normal to a neoplastic cell or the de novo manifestation of a neoplastic cell, and that the generic substance could potentiate the possible metastatic development after that (in certain cases) [10,11]. The number of scientists supporting the claim that the occurrence of melanomas after taking the relevant medication is a sporadically conditioned fact or a pure coincidence is decreasing more and more.

The shared data regarding the role of nitrosamines in the generation of skin cancer are based on single, but now dozens of case reports [1-9]. However, these data are also supported by a large-scale study regarding the follow-up and analysis of patients taking NDMA-contaminated valsartan versus those taking uncontaminated medicinal products containing valsartan again [12]. The conclusion of their analyzes postulated the following: there was a minimal but statistically significant risk of developing melanoma and liver cancer in the group of patients taking NDMA-contaminated valsartan [12].

We present the first case in the world literature of a patient who took potentially nitrosamine/s-contaminated candesartan and developed melanoma in situ, thin melanoma in close proximity, and a dysplastic nevus simultaneously and within the framework of this intake. The two melanoma-suspicious lesions were surgically removed in one stage with a margin of surgical safety of 2 cm in all directions. The potential role of nitrosamines as generators for melanomas and/or melanoma precursor lesions is discussed.

Case report.

We are reporting on a 67-year-old female patient who presented to the outpatient clinic regarding a mole above the left breast, which has changed its shape and color over the past 2.5-3 years. The history of this lesion is about no more than 10 years according to the history. In parallel with this, for 3 years the patient has been diagnosed with arterial hypertension, treated during this period (and at the moment) with Candesartan 16 mg once daily. Drug intake is irregular, and the patient takes monthly breaks of at least 4-5 days.

During the ambulatory examination, the presence of two pigment lesions in close proximity to each other, located above the left breast, was found (Figure 1a). In the first lesion, a pigmented, slightly asymmetric lesion is observed, with vaguely limited boundaries in the periphery, bicolor, slight elevation in places, as well as dermatoscopically: central regression in the form of gray white structureless areas, disturbed pigment network, brown to black color. Clinically and dermatoscopically, a lentiginous coating is also observed, which connects this lesion with a second, newly appearing pigmented one (lesion), at a distance of no more than a few millimeters.

The clinical and dermatoscopic findings of the second lesion were suggestive of a thin melanoma or severe dysplastic nevus adjacent to the first lesion (Figure 1a). Surgical treatment was performed for both lesions in a single surgical session with a surgical margin of safety of 2 cm in all directions (Figure 1b).

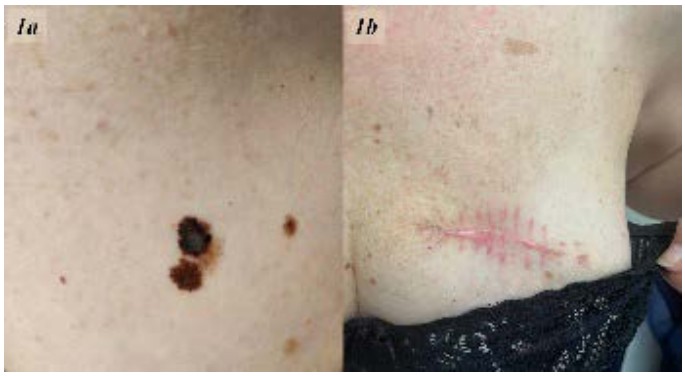

Figure 1. *1A: Melanoma in situ and thin cutaneous melanoma connected with lentiginous proliferation between them. 1B: Postsurgical result after 1 month.*

The histopathological findings of the first lesion showed evidence of: an extensive, poorly demarcated melanocytic lesion represented by ortho- and follicular hyperkeratosis, proliferation of atypical fusiform melanocytes forming an ascending migration with consumption of the overlying epidermis, and horizontal confluence of the distal parts of the epidermal ridges, demarcated by lichenoid, angiofibroplastic stroma with many melanophages causing marked regression (2a,2b). Clean resection lines. The histological pattern corresponds to malignant melanoma in situ (2a,2b). Marked regression of the lesion does not allow assessment of the presence of a dermal component.

The postoperative performed computed tomography of the whole body (with contrast) showed no evidence of the presence of metastases. The patient was staged as stage 1a melanoma and candesartan was discontinued. She was referred for follow-up to the regional cancer dispensary at her place of residence.

During the post-operative follow-up examination one month later, a new pigmented lesion was found in the area of the back skin below the left scapula, corresponding clinically and dematoscopically to a dysplastic nevus (Figure 3a,3b). Surgical removal of the lesion is recommended.

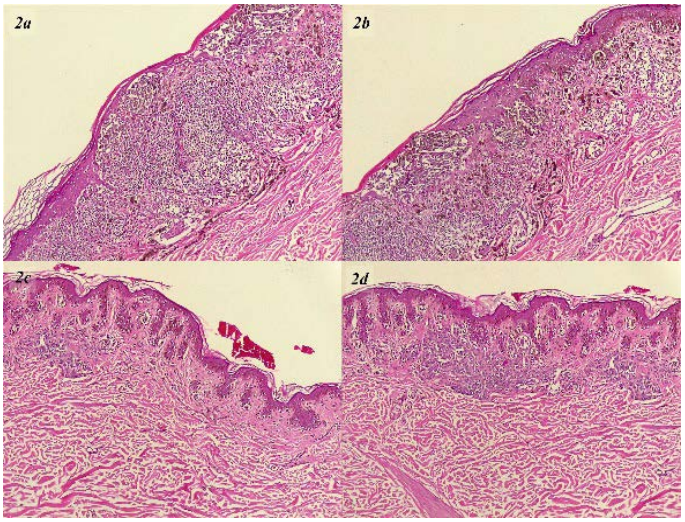

Figure 2*. 2a/b: HE x 100 magnification- melanoma in situ with prominant regression. 2c: HE x 40 magnifications: superficial spreading melanoma with peripheral lentiginous proliferation (branching the adjustant melanoma in situ). 2d: HE, x100 magnification- superficial spreading cutaneous melanoma*

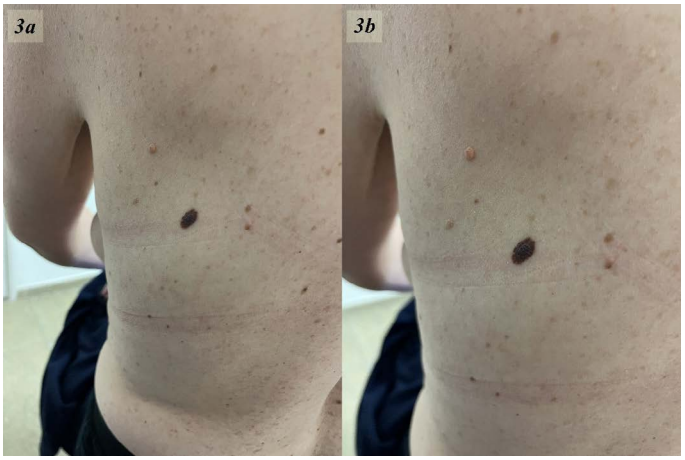

Figure 3. *During the post-operative follow-up examination one month later, a new pigmented lesion was found in the area of the back skin below the left scapula, corresponding clinically and dematoscopically to a dysplastic nevus.*

Discussion.

The most recent analysis of patients who took NDMA-contaminated valsartan and subsequently developed melanomas is, in all likelihood, ″another not unimportant link″ in the puzzle of carcinogenesis concerning skin cancer, but not only [12].

Unfortunately, these data do not specify whether the concentration of NDMA in valsartan is above the so-called daily acceptable intake dose /ADIs or many times above it [12]?

As well as second: they do not include and analyze a drug product contaminated with another type of nitrosamine/s, again containing valsartan. In practice, this is a limited but at the same time indicative analysis that contains alarming data and undoubtedly arouses interest in future follow-ups [12]. From an ethical point of view, these follow-ups cannot be of a prospective nature, which in practice is also a ″serious shield″ for the pharmaceutical companies.

Considering that over 80% of melanomas are due to acquired mutations (as a result of exposure to currently completely unclear carcinogens/mutagens), monitoring mono- and poly-contamination with nitrosamines could possibly clarify a significant number of issues concerning the pathogenesis of skin cancer , but also on a global scale regarding cancer in general.

Polycontamination with up to three nitrosamines in sartans (in one tablet) is also a well-known fact, officially presented by the regulatory authorities in the face of the FDA/EMA. Promises from about a year and a half ago that the concentration and type of relevant mutagen/nitrosamine would be declared in the package leaflet remain to this day ″slightly forgotten″ or more a myth than a reality in some European countries.

The question remains open: What should be the exact interpretation of the ″gesture″ of the pharmaceutical companies themselves to quickly withdraw their ″safe products/ preparations″ from the drug market, which contain from 20 to 200 times increased concentrations of mutagens above the permissible daily dose for example [13]?

It is not a secret that the systemic administration of ARBs/ sartans as monotherapy could be problematic [14]. That is why a publication in the magazine Lancet was hinted at back in 2010 [10]. It specifically linked the use of sartans with a negligible but still statistically present risk of developing cancer in ``human beings in general, not in vitro or in animals [15]. But at the time, the problem with the Nitrosamine contamination was unknown.

12 years later, the suspicion of a link between Sartans and Cancer turns out to be more than current, as the data of the same authors are categorical/confirmatory in favor of the fact that their three-year cumulative intake could be associated with a significant risk of the development of all forms of cancer [16].

Unfortunately, the problem with nitrosamines became public only in 2018, and in practice it gives a more than eloquent, albeit indirect, explanation of the question: "What is the cause of the cancer pandemic in recent decades?". A landmark publication by Beatrice Nardone et al. from 2017 [17] returns the dilemma of the role of ARBs/ Sartans as monotherapy and the risk of developing melanomas as completely real and possible: unadjusted OR (95 % CI): 2.25 (1.73-2, 94)/adjusted OR (95% CI): 1.24 (0.54-2.85) [17].

Percentagewise, this risk varies for melanomas in particular between 24% and 224% [17].

A new French study find out similar observations, finding about a 10% risk of developing melanomas when taking NDMA-contaminated valsartan [12].

Dwelling on Beatrice Nardone's table, the following is striking [17]:

There is a risk of developing melanomas after the administration of ACE inhibitors, Sartans and thiazide diuretics. This risk varied between 24% for sartans, 182% for thiazide diuretics and 171% for ACE inhibitors. It is unlikely to hypothetically impossible that this risk is due to the mechanism of action of the main substance of the medication. The table shows that the risk of developing basal cell carcinoma is similar and significantly higher than that of developing melanomas, namely: 223% for ACE inhibitors, 286% for ARB blockers and 211% for thiazide diuretics [17].

For the development of squamous cell carcinomas, the risk varies and is as follows: 194% for ACE inhibitors, 222% for ARB blockers and 411% for thiazide diuretics [17].

Bearing in mind that batches of precisely these three classes of drugs have been withdrawn from the market due to contamination with nitrosamines, it should not be difficult to answer the questions:

1) ″Is there any evidence to support the presence of a particular carcinogen in all three classes of drugs?″

2) ″Is there a carcinogen or mutagen that could be considered responsible for the generation of all three types of skin cancer: basal cell carcinoma, squamous cell carcinoma, and melanoma?″

3) In practice, is there data in the whole world literature for exactly this type of mutagen/ carcinogen that has been identified as contamination in doses exceeding from 20 to 200 times the maximum permissible for the day and are described as potentially carcinogenic?

The problem regarding the exact identification of mutagens/ carcinogens (the so-called nitrosamines) and their relationship with skin cancer and melanomas in particular, turns out to be real and is further deepened by:

1) The lack of any official regulatory data (skin cancer and cancer in general after intake of potentially nitrosamine-contaminated medicinal products) from large geographic regions such as Africa, South America, the Balkans, North Korea, the Russian Federation, parts of Asia , India, and former Soviet republics. Regions where all these medications are widely distributed, but also regions where, in all probability, the problem of focusing on this problem turns out to be less of a priority. In certain European countries, there is a lack of official inspections and the announcement of their results when reports are filed for more than 32 companies distributing potentially contaminated preparations. Preparations after the use of which side effects such as skin cancer, but not only, have been described. All of these side effects have been documented in reputable scientific journals [3].

1) The lack of official data from the regulatory bodies themselves regarding: the type of nitrosamine/the number of nitrosamines and its/their exact concentrations in many/ some of the currently distributed medicinal preparations remains puzzling and worrying to say the least. In practice, companies are currently not obliged (in some countries) to declare the nitrosamines distributed by them, which are also recognized as possible human carcinogens [18].

Future observations on melanomas arising after taking high blood pressure preparations (but not only) contaminated with up to 3 nitrosamines simultaneously should be accompanied by mutational analysis of melanomas with a view to elucidating the

pathogenetic role of these mutagens. Over 80% of melanomas are due to acquired mutations as a result of exposure to possibly currently unknown exogenous mutagens.

The disclosure of nitrosamine contamination by the FDA in 2018 may also be the first major step in solving the problem of acquired mutations and cancer pathogenesis in general on a global scale.

The redeployment of nitrosamine-contaminated production batches of drugs to regions with weak to no regulatory control should not be a priority for the ethical and legal norms of regulatory bodies, pharmaceuticals, and clinicians in general.

Advances in medicine could very often be driven by conclusions based on negative observations or side effects.

The complex analysis of these data could become the most powerful preventive tool of the planet in the fight against cancer in general, only when the postulate is followed: ″First, do no harm!″ ...and : ″Analyze first. before doing anything else...″

Because progress is often associated with discomfort ...for someone and for something...?!.

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