GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 2 (347) Февраль 2024

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.

GEORGIAN MEDICAL NEWS
No 2 (347) 2024

Содержание:

GEORGIAN MEDICAL NEWS
No 2 (347) 2024

DRUG RELATED NITROSOGENESIS, PHOTOCARCINOGENESIS AND ONCOPHARMACOGENESIS OF NODULAR MELANOMA: A CASE RELATED ANALYSIS CONCERNING THE POLYCONTAMINATION OF THE POLYMEDICATION WITH VALSARTAN/HYDROCHLOROTHIAZIDE AND BISOPROLOL

Tchernev G[1,2], Broshtilova V[3], Ivanov L[2], Alexandrov A[2], Smilov N[4], Kordeva S[1].

[1]*Onkoderma- Clinic for Dermatology, Venereology and Dermatologic Surgery, General Skobelev 26, 1606 Sofia, Bulgaria.*

[2]*Department of Dermatology and Venereology, Medical Institute of Ministry of Interior General Skobelev 79, 1606 Sofia, Bulgaria.*

[3]*Department of Dermatology and Venereology, Military Medical Academy, 1606 Sofia, Bulgaria.*

[4]*Director of the Medical Insitute of Ministry of Interior, Medical Institute of Ministry of Interior, General Skobelev 79, 1606 Sofia, Bulgaria.*

Abstract.

Despite the fact that the pathogenesis of cutaneous melanoma is shrouded in mystery, factors that have been neglected or unnoticed until now have come to the attention in recent years, and in all likelihood, they could also be pivotal. These factors, known as nitrosamines or NDSRIs, are characterized by high carcinogenic and mutagenic potency, and some of them have demonstrated these properties to human DNA as well. Unfortunately, these ingredients also turn up as contaminants in about 300 of the most widely distributed drugs worldwide.

According to the most recent literature, some of these ingredients are also identified as potent photocarcinogens, as well as human carcinogens.

The intake of these carcinogens in the context of polycontamination of polymedication, has been associated for years with the occurrence of melanomas.

The need for cataloguing of nitrosamines , as well as their accurate labelling on drug packaging, would help to classify them even more accurately as carcinogens affecting human DNA.

We present once again a patient , who developed nodular melanoma within the context of the intake of 3 potentially nitrosamine/ NDSRIs contaminated antihypertensive drugs (valsartan/ Hydrochlorothiazide/ bisoprolol). Pathogenetic aspects concerning drug-induced nitrosogenesis, photocarcinogenesis and oncopharmacogenesis of skin cancer are discussed.

Nitrosogenesis' of Cancer as concept in the medical literature has been known for decades, but in relation to other forms of human cancer. Exogenously mediated drug-mediated nitrosogenesis is a logically conditioned and newly defined concept whose significance with respect to the clinical manifestation of skin cancer is only beginning to grow.

Key words. Valsartan, HCT, nodular melanoma, nitrosogenesis, oncopharmacogenesis, sartans.

Introduction.

Melanoma is a multifactorial disease with a complex and somewhat mysterious origin. The pathogenesis of melanoma remains enigmatic; however, acquired mutations involving the RAS oncogenes and p53 are among the key factors contributing to its development [1]. Approximately 2% of all skin malignancies are attributed to melanoma [2]. Despite its relatively low percentage, its impact on mortality rates is significant, making it a major public health concern [2].

The uncertainty surrounding the pathogenesis of this group of neoplasms has been partially unraveled, revealing the presence of potent/actual mutagens and carcinogens worldwide, including nitrosamines found in various drug classes [3]. Initially, the FDA announced several recalls of ARBs (sartans), specifically valsartan, losartan, and irbesartan [4], due to nitrosamine contamination concerns. Currently, an increasing number of medications are being identified and added to the list of potentially/actually contaminated drugs [5].

The issue of polycontamination in polymedicated and polymorbid patients remains unresolved, particularly regarding the cumulative effects of mutations on the human genome. In this context, we discuss the potential occurrence of nodular melanoma in relation to polycontamination during 10-15 years of systemic antihypertensive therapy with valsartan/ hydrochlorotiazide, valsartan, and bisoprolol.

These medications used as monotherapy are already recognized as being contaminated with nitrosamines by the regulatory authorities [4,5]. We believe that the cumulative effect of the different medications taken over the years potentially/actually contributed to the development of nodular melanoma. With the following case report, we are once again addressing this serious issue and ensuring it receives the attention it deserves.

Case report.

A 76-year-old male presented to the dermatology department with primary complaints of a tumor formation located on the back, first noticed approximately a year ago prior to the consultation. The lesion has gradually grown over time, and in the last two weeks, it has also started to bleed upon touch.

The patient has a history of liver hemangioma, which he checks annually; mitral valve replacement performed 5 years ago followed by therapy with acetylsalicylic acid 100 mg once at night; and a partial resection of the prostate conducted 10 years ago. He also reports arterial hypertension, which he manages with valsartan/hydrochlorothiazide 160 mg/12.5 mg administrated once in the morning for the past 10 years. In the summer season, he switches to valsartan 160 mg once daily in the morning. Additionally, he takes bisoprolol fumarate half a tablet twice daily, a regimen he has followed for the past 15 years.

The patient requested physical evaluation of the lesion and further therapeutic approach to be established.

The dermatological examination revealed a dark brown pigmented lesion with uneven borders and pigmentation

observed in the area of the back. The lesion was measured 1.5 cm in diameter and covered with hemorrhagic crust. The clinical and dermatoscopic picture was suspected for cutaneous melanoma from nodular type.

Routine blood tests were performed resulting without abnormalities. The patient was recommended surgical removal of the lesion under local anesthesia. After consultation with a cardiologist, the anticoagulant therapy was discontinued 5 days prior to the surgery and was replaced with fraxiparine 0.4 subcutaneous injections administrated twice, 48 hours before the surgery. S-100 protein levels were examined and found to be negative.

The lesion was preoperatively marked (Figure 1a). Following thorough disinfection of the operative field under local anesthesia with lidocaine 1%, an elliptical excision was carried out with a safety margin of no more than 5 mm in all directions (Figure 1b). The wound edges were adapted with single interrupted sutures (Figure 1c), and a sterile dressing was applied. The histopathology revealed an extensive, symmetrical, well-demarcated melanocytic lesion with epidermal necrosis and covered with parakeratotic crust. A compact proliferation of large, atypical melanocytes was observed, characterized by marked pleomorphism, centrally located nuclei with 1-2 nucleoi, and formation of atypical mitoses. Additionally, areas of desmoplastic degeneration and moderately expressed lymphocytic, well-vascularized, melanophage-rich stroma were identified (Figures 2a,b). The resection margins were clear, and there was no evidence of perineural or lymphovascular invasion. A diagnosis of nodular melanoma with ulcerations, staged T3bN0M0, Clark level 3 and Breslow tumor thickness of 2.5 mm was established. The mitotic index was noted to be 5-5/field.

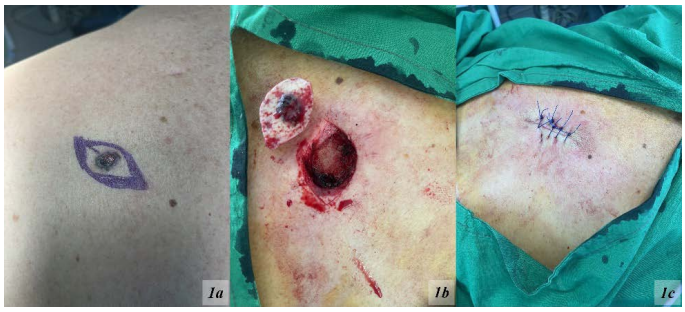

Figure 1a-c. *Intraoperative view: surgical removal of the melanoma lesion.*
1a: *The lesion is preoperatively marked.*
1b: *Elliptical excision of the suspected melanoma lesion.*
1c: *The wound edges were adapted with single interrupted sutures.*

The patient was referred for a reexcision with 1.5 cm in all directions, followed by detection and potential removal of a sentinel lymph node.

Discussion.

Characterized by rapid distant metastasis and high mortality rates, cutaneous melanoma has earned its problematic reputation among the other types of skin cancer [6]. Standard treatment therapies for arterial hypertension often include ACE inhibitors and ARBs [6]. Their long-term effects on the skin continue to be a subject of debate and controversy within the dermatological community [7].

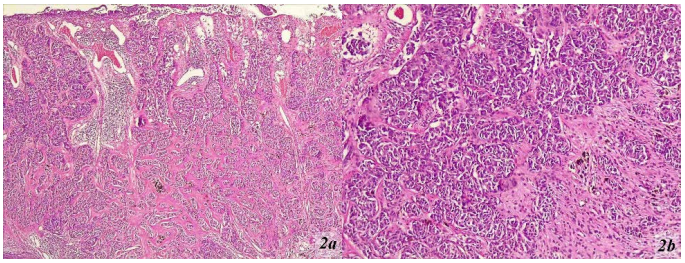

Figure 2a,b*. Histopathological findings.*
2a: *Nodular melanoma x100 – ulcerated epidermis with dense dermal infiltration of atypical and severely pleomorphic melanocytes, forming polycyclic nests among angiofibrotic stroma.*
2b: *HEx200 – severely pleomorphic melanocytes with large nuclei and dusty cytoplasms.*

Becker et al. [6]. have associated ACE inhibitors, such as lisinopril, and ARBs (sartans), such as losartan, with the stimulation of MV3 melanoma cell migration and invasion. This "phenomenon" or "pure coincidence" is no longer considered by the community as a myth; rather, it is increasingly recognized as a possible pathogenetically determined relationship especially because of the Nitrosamine contamination issue [7].

The FDA has recently identified potential carcinogens in over 250 currently available drugs, categorizing them based on their carcinogenic potency, with classifications ranging from 1 (lowest) to 5 (highest) [5]. In 2019, the FDA updated its table of initial limits for nitrosamine impurities (NDMA, NDEA, and NMBA) in sartans [4]. Valsartan, as mentioned in our case report, is currently on the list of drugs officially recalled by the FDA due to nitrosamine impurities [4]. Hydrochlorothiazide (N-nitroso-hydrochlorothiazide) is listed under potency category 4 with recommended AI limit of 1500 ng/day [5]. Recently, the pharmaceutical company Pfizer initiated recalls of INDERAL LA (Propranolol hydrochloride) due to the presence of N-nitroso-propranolol, impurity which has the potential to probably potentiate the carcinogenesis [12]. Based on the above, beta blockers have already been considered in the category of medications with permissive availability for nitrosamines [5]. And following the FDA list, bisoprolol (N-nitroso-bisoprolol) is being currently listed under potency category 4, with a recommended AI limit of 1500 ng/day [5]. Each of the mentioned medications impurities is listed under a special grade potency category/ carcinogenic potency, making the medication itself more carcinogenic. During a certain period, the patient mentioned in our case report was undergoing combined therapy with valsartan/hydrochlorotiazide or valsartan as monotherapy for 10 years and bisoprolol for almost 15 years. Therefore, the cumulative effect of each drug and the possible nitrosamine/ NDSRIs contaminants become a more probable, relatable, and adequate cause for the development and progression of nodular melanoma. The conclusion is not based on hypothesis but rather on evident clinic-pathological correlations between the timing and duration of medication intake, particularly those already recognized by the authorities as potentially/actually contaminated with nitrosamines [4,5], and the subsequent development of skin cancer.

Nitrosamine-contamination in different antihypertensive medications (and now not only) has become a reality, marking the

beginning of what some authors refer to as the "Nitrosogenesis era″ [10]. The term "Exogenous, drug mediated Nitrosogenesis" has recently surfaced in the medical literature, referring to nitrosamines or nitrosamine drug-substance-related impurities (NDSRIs) within polycontamination among polymorbid patients [10]. The concept suggests that when individuals are exposed to multiple carcinogens, as in the context of polymedication, the possible cumulative effect (carcinogenic/ mutagenic or genotoxic one) can act as the triggering point for the development and/or progression of skin cancer [10].

Given the widespread use of drugs for hypertension among the population, it is reasonable to assert that the potential/actual exposure to nitrosamines in medications is playing a significant role in the emergence of the new "cancer pandemic".

Conclusion.

The current global issue with drug-induced cancers development and progression in the context of Nitrosogenesis/ Onco-pharmacogenesis, particularly skin cancer following oral intake of certain antihypertensive medications, is prompting clinicians to address the issue more comprehensively.

Effective strategies for tackling this global problem are being made through various case reports, letters, interviews, congresses/congress reports, etc.

A number of large cross-national follow-up studies have found a significant association between intake of a heterogeneous class of antihypertensive drugs and the development of melanomas [13-16], but the lack of precise information on potential contamination prevents the most accurate interpretation of the data.

These correlations strongly suggest a link between the timing of medication intake and the onset/development of the tumorous skin lesions.

Dealing with NDSRIs poses a significant challenge due to the difficulty in distinguishing whether the ingredients within the medication possess mutagenic, carcinogenic, or both effects. Regardless, prioritizing the removal of such impurities should be a priority, and regulatory bodies must take a more assertive approach in addressing this global issue.

Interesting , but at the same time extremely alarming, remains recently shared scientific data that allow certain nitrosamines such as N-nitrosomorpholine to be classified also as potent photocarcinogens with marked genotoxic effects [18]. Photocarcinogenesis and nitroso-photocarcinogenesis appear to be practically inextricably connected [19].

Nitroso-photocarcinogenesis is a fact that should be studied in detail in the near future.

Nitrosamines in tobacco, such as Nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-butanone (NNK), have been shown to have mutagenic effects on human DNA, affecting RAS oncogenes and p53 [18]. The same target genes remain pathogenetic for the majority of melanomas [1]. The potential contamination of sertraline with NNK-type NDSRIs, for example, is now associated with the clinical generation of melanomas in humans [20].

The gross overlap of target genes (in the first reading) that are key to melanomas but are also attacked and mutagenically affected by nitrosamines is concerning to say the least.

Future analyses should focus on elucidating the phototoxicity of the NDSRIs contained in the drugs as well as the mutations they induce in patients with melanomas but also those with skin cancer in general.

Photo-nitrosogenesis in the context of Oncopharmacogenesis are and would be a good explanation of the relationship: polymedication/polycontamination and skin cancer / melanoma generation. Evidentiary steps in this direction are given at first but should be confirmed in future follow-up and subsequent analyses.

REFERENCES

1. Bardeesy N, Bastian BC, Hezel A, et al. Dual inactivation of RB and p53 pathways in RAS-induced melanomas. Mol Cell Biol. 2001;21:2144-53.

2. Linares MA, Zakaria A, Nizran P. Skin Cancer. Prim Care. 2015;42:645-59.

3. Tchernev G, Kordeva S, Marinov V, et al. Nitrosamines in antihypertensives, metformin and raniti-dine as cofactors for melanoma and development of other cancers. Expert group opinion. Port J Dermatol and Venereol. 2022;80:332-334.

4. https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan

5. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/updated-information-recommended-acceptable-intake-limits-nitrosamine-drug-substance-related

6. Becker Y, Stock C. The ACE Inhibitor Lisinopril Stimulates Melanoma Cell Invasiveness by Inducing MMP2 Secretion. Cell Physiol Biochem. 2022;56:457-483.

7. Tchernev G, Kordeva S, Patterson JW. Nitrosamines and skin cancer: rather reality than a myth? J Med Review (Bulgarian). 2023;59:5-7.

8. Tchernev G, Oliveira N, Kandathil LJ, et al. 4th National Congress of the Bulgarian Society for Dermatologic Surgery, Sofia, 12th March 2022 with main topics: one step melanoma surgery and drug induced melanoma. Dermatol Reports. 2022;14:9542.

9. Kordeva S, Cardoso J, Tchernev G. Congress report of the 5th national congress of the bulgarian society for dermatologic surgery, sofia, 11th march 2023 with main topics: nitrosamines as most powerful trigger for skin cancer development and progression/personalised one step melanoma surgery as possible skin cancer treatment option. Georgian Med News. 2023;337:89-95.

10. Tchernev G. 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. Georgian Med News. 2023;339:83-88.

11. Tchernev G, Temelkova I. Valsartan Induced Melanoma?! First Description in Medical Literature! Open Access Maced J Med Sci. 2018;6:2378-2380.

12. https://recalls-rappels.canada.ca/en/alert-recall/pfizer-recalls-inderal-propranolol-hydrochloride-capsules-due-nitrosamine-impurity

13. Mansouri I, Botton J, Semenzato L, et al. N-nitrosodimethylamine-Contaminated Valsartan and Risk of Cancer: A Nationwide Study of 1.4 Million Valsartan Users. J Am Heart Assoc. 2022;11:e8067.
14. Nardone B, Majewski S, Kim AS, et al. Melanoma and Non-Melanoma Skin Cancer Associated with Angiotensin-Converting-Enzyme Inhibitors, Angiotensin-Receptor Blockers and Thiazides: A Matched Cohort Study. Drug Saf. 2017;40:249-255.
15. Azoulay L, St-Jean A, Dahl M, et al. Canadian Network for Observational Drug Effect Studies (CNODES) Investigators. Hydrochlorothiazide use and risk of keratinocyte carcinoma and melanoma: A multisite population-based cohort study. J Am Acad Dermatol. 2023;89:243-253.
16. Schmidt SA, Schmidt M, Mehnert F, et al. Use of antihypertensive drugs and risk of skin cancer. J Eur Acad Dermatol Venereol. 2015;29:1545-54.
17. Mochizuki H, Nagazawa Y, Arimoto-Kobayashi S. Genotoxicity and the stability of N-nitrosomorpholine activity following UVA irradiation. Mutat Res Genet Toxicol Environ Mutagen. 2024;893:503721.
18. Stanfill SB, Hecht SS, Joerger AC, et al. From cultivation to cancer: formation of N-nitrosamines and other carcinogens in smokeless tobacco and their mutagenic implications. Crit Rev Toxicol. 2023;53:658-701.
19. Tchernev G, Naydekova N, Ivanov L, et al. Enigmatic lessons from Dermatologists: Pharmacooncogenesis and Nitrosogenesis of Skin Cancer: Facts and Controversies. J Medical Review (Bulgarian) 2024;60.
20. Tchernev G. Nitrosogenesis, antidepressants and the sertralin induced nevus associated cutaneous melanoma: the ndma/ nnk (ndsris) contamination as most potent melanoma inductors: alea iacta est. Georgian Med News. 2023;342:47-53.