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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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SECONDARY AMINO GROUPS IN ACE INHIBITORS/ CALCIUM CHANNEL BLOCKERS, ANTIARRHYTHMICS AND ANTICOAGULANTS AS DONORS FOR DRUG RELATED PHOTOTOXICITY/ CARCINOGENICITY : NUTRITIONAL NITROSOGENESIS AS SUBSTANTIAL/ ADDITIONAL COFACTOR FOR SKIN CARCINOGENESIS

Tchernev G[1,2]*, Kordeva S[1], Broshtilova V[3], Tchernev KG Jr[2].

[1]Department of Dermatology and Venereology, Medical Institute of Ministry of Interior
General Skobelev 79, 1606, Sofia, Bulgaria.
[2]Onkoderma- Clinic for Dermatology, Venereology and Dermatologic Surgery, General Skobelev 26, 1606 Sofia, Bulgaria.
[3]Department of Internal Diseases, Pharmacology and Clinical Pharmacology, Pediatrics,
Epidemiology, Infectious Diseases, and Skin Diseases Faculty of Medicine, Sofia University Saint KlimentOhridski, Bulgaria.

Abstract.

Drug-mediated phototoxicity and photocarcinogenicity have long remained poorly understood. One of the most significant dilemmas surrounding this issue is the sporadic nature of these reactions.

This sporadic occurrence may be explained by modern and newly introduced concepts such as drug-mediated nitrosogenesis of skin cancer, as well as nitroso-photocarcinogenesis of skin cancer. Regardless of their carcinogenic potential, all nitrosamines may exhibit phototoxic properties and may therefore act as photocarcinogenic substances, because of the instability of the nitroso group under UV radiation.

Drug-related Nitroso Photocarcinogenesis represents a new and innovative concept that seeks to provide a logical explanation for the phenomenon of nitroso-photocarcinogenicity.

Various groups of medications, including antihypertensive agents (beta-blockers, ACE inhibitors, calcium antagonists, centrally acting sympatholytics, and sartans), anticoagulants, antidiabetic drugs, and several other classes, possess secondary amino groups. Under gastric conditions - an acidic environment and in the presence of nitrite-rich food - these amino groups may lead to the formation of nitrosamines, which are well known carcinogens and established photocarcinogens. The subsequent resorption of these drug-mediated nitroso compounds may result in their subsequent deposition in the skin.

The decomposition of nitrosamines under the influence of ultraviolet radiation may lead to the release of nitric oxide and/ or procarcinogenic mediators capable of damaging DNA of keratinocytes and melanocytes. Thus, in practice, malignant cellular branches may be initiated even when the relevant groups of medications are not externally contaminated with nitrosamines. In this sense, generic drugs from heterogenous classes may effectively act as donors of photocarcinogenic compounds to the human skin.

In this context, and in support of the aforementioned modern concept of skin cancer, we present another case of keratinocyte cancer (basal cell carcinoma) that developed relatively shortly after combined intake of four drugs (apixaban, flecainide, amlodipine, and perindopril), each containing a secondary amino group in its structure - serving as a potential precursor for the generation of photocarcinogens in the stomach.

The skin cancer has been removed surgically. The defect has been treated via nasal tip rotation flap as dermatosurgical approach.

The role of endogenous, gastric related Nitrosogenesis during intake of potentially completely uncontaminated drugs (containing secondary amino groups in their chemical structure), in relation to nitroso-photocacinogenesis and the subsequent development of skin cancer, is discussed.

Key words. Apixaban, flecainide, N-nitroso-flecainide, amlodipine, N-nitroso-amlodipine, perindopril, N-nitroso-perindopril, N-nitrosamines, secondary amines, polymedication, nitrosogenesis, nitroso-photocarcinogenesis, keratinocyte cancer, basal cell carcinoma, dermatosurgery, reconstructive surgery, nasal tip rotation flap.

Introduction.

Nitrosamines have been discussed since the 1930s as photolabile compounds, characterized by their ability to undergo photodegradation/photodecomposition regardless of their carcinogenic potential [1]. N-nitosodimethylamine (NDMA) for example, as well as other N-nitrosamines, can undergo fragmentation of the N-N bond, which is unstable under ultraviolet irradiation [1,2].

The mechanism of carcinogenicity for many nitrosamines is already unraveling its mystery, making it rather a reality than a myth [3].

Some nitrosamine impurities can be formed in the active pharmaceutical ingredient during external synthesis, including during manufacturing or storage, and may consequently be present in finished pharmaceutical preparations [4].

However, another form of endogenous nitrosamine formation may occur through the intake of medications containing secondary and tertiary amino groups, such as ACE inhibitors [5], calcium antagonists [6], beta-blockers [7], sartans, metformin, etc. [8].

Upon exposure to an acidic environment and in the presence of nitrite-rich food, these drugs (containing secondary amines) may form nitrosamines in the stomach [9]. This process can occur even when the drugs are completely free of exogenous nitroso contamination. Subsequent resorption of the nitroso compounds may lead to increased concentrations in the bloodstream, with two possible outcomes:

1) The nitrosamines may undergo metabolic activation in the liver through enzymatic alpha-hydroxylation with cytochrome P450, resulting in dealkylated primary nitrosamine (2). This product is unstable and subsequently decomposes to form a diazoniumion - a DNA alkylating agent (2). The resulting DNA damage can lead to carcinogenesis (2).

2) Within the established bioavailability of nitroso compounds in peripheral blood, and when they are not metabolically activated in the liver, nitrosamines may exert genotoxic and phototoxic effects, when deposited on skin and following photodecomposition, NO release, ROS interaction, and subsequent DNA damage [10,11].

The question of whether a certain drug product is entirely free from nitrosamine contamination may now be of limited significance. The newer concept extends beyond the presence of preformed nitrosamines in medications as potential carcinogenic agents and also considers the structural components of drug molecules that may act as precursors for their endogenous formation within the body. This so-called endogenous nitrosamine formation concept proposes that certain pharmaceutical compounds may contribute to carcinogenesis through in vivo generation of nitrosamines, potentially playing a role in the development of skin cancer.

We present another case of a patient who developed basal cell carcinoma located on the apex nasi, which was surgically excised and subsequently reconstructed using a nasal tip rotation flap. The skin cancer development followed the start of the long-term systemic therapy for arterial hypertension with apixaban, flecainide, amlodipine, and perindopril. All of these medications contain secondary amino groups that, under gastric conditions, could can react with nitrites from food to form N-nitrosamines, with or without prior hepatic metabolism, thereby supporting the concept of endogenous nitrosamine formation.

Additionally, flecainide, amlodipine, and perindopril contain N-nitrosamine impurities, representing a risk for exogenous intake.

This bi-/poly-contamination may represent a possible factor contributing to: 1) accelerated cancer development or progression, with or without the presence of polymedication, or 2) the sporadic occurrence of cancer in certain individuals, potentially explaining why some patients develop more aggressive or more rapidly progressing malignancies that others.

Case report.

A 64-year-old male presented with the primary complaint of a tumorouslesion on the nose, first noticed approximately 3-4 years prior to consultation, withgradual enlargement, ulceration, and bleeding observed over the past one year.

The patient had a medical history for arterial hypertension and was receiving long-term systemic therapy consisting of apixaban 5 mg twice daily, flecainide acetate 100 mg twice daily, amlodipine 5 mg (half a tablet in the morning and one in the evening), and perindopril arginine 5 mg - once in the morning. These medications had been administered for approximately 3-4 years.

The patient was an indoor mechanic, with no history of sunbathing or significant chronic sun exposure. He was classified as Fitzpatrick skin type III. No relevant history of sun exposure was identified.

Dermatological examination revealed an achromatic tumorous lesion protruding above the surrounding skin, with irregular borders and visible telangiectasias, located on the apex nasi (Figure 1). Based on the clinical presentation, basal cell carcinoma was suspected. Enlarged lymph nodes were not palpable.

Routine laboratory tests showed mild abnormalities consistent with dyslipidemia. The patient was recommended for surgical excision of the lesion.

Following cardiology consultation, the patient's anticoagulant therapy with apixaban was temporarily replaced with nadroparin calcium 0,6 ml administered subcutaneously during the period of hospitalization.

The tumorous lesion located on the apex nasi was preoperatively marked with 0.2 mm safety margins in all directions. Primary closure of the resulting defect was not feasible due to the tension generated in this region, the nose representing a major aesthetic unit and a sensitive anatomical area due to its structural complexity and cosmetic significance. A skin graft was considered unsuitable due to the likelihood of visible discoloration and poor tissue match. Therefore, reconstruction with a local skin flap was preferred.

The team opted fora nasal tip rotation flap (Figure 2a). The flap was designed as a medially based superior arc of rotation intended to rotate the entire nasal tip. The incision is placed between the nasal tip and dorsum subunits. A Burow's triangle was created perpendicularly and inferiorly on the contralateral side. An additional Burow's triangle was excised from the distal part of the arc, positioned superior to the arc. This triangle was carefully aligned parallel to the alar rim to prevent facial disfigurement.

The flap was then excised and elevated, followed by undermining of the entire nasal tip just superficial to the perichondrium (Figure 2b,c). After confirming the resulting tension vectors would be evenly distributed, the tissue was carefully rotated to cover the primary defect. The first sutures were placed at the inferior Burow's triangle to further reduce the tension. The remaining closure of the secondary defect was completed using single interrupted sutures (Figure 3).

The histopathological examination revealed a nodulocystic type of basal cell carcinoma, with infiltration of the lateral resection margin, corresponding to stage 1 pT1NxMxR1. Adjuvant radiotherapy was recommended following suture removal. Due to postoperative edema observed in the facial region, therapy was initiated with methylprednisolone i.v. 16mg for four days, famotidine 40 mg twice daily, levocetirizine dihydrochloride 5mg per os once daily, and local application of cool packs.

Discussion.

C. Crews [12] have described three main classes of nitrosamines: 1) Volatile N-nitrosamines - lower molecular weight compounds formed from secondary amines; 2) Non-volatile N-nitrosamines - compounds that can be extracted from foods, and 3) Total N-nitrosamine content - a combined measure of both volatile and non-volatile N-nitrosamines, also including unidentified molecules, such as nitrosated proteins that have not

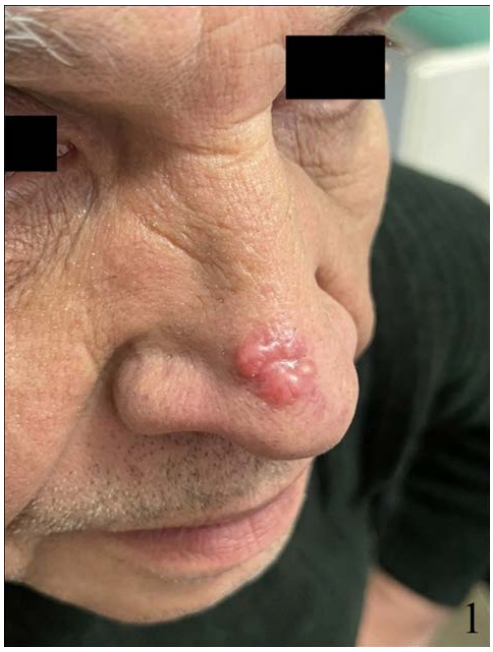

Figure 1. *An achromatic tumorous lesion protruding above the surrounding skin, with irregular borders and visible telangiectasias, located on the apex nasi, clinically suspected for basal cell carcinoma.*

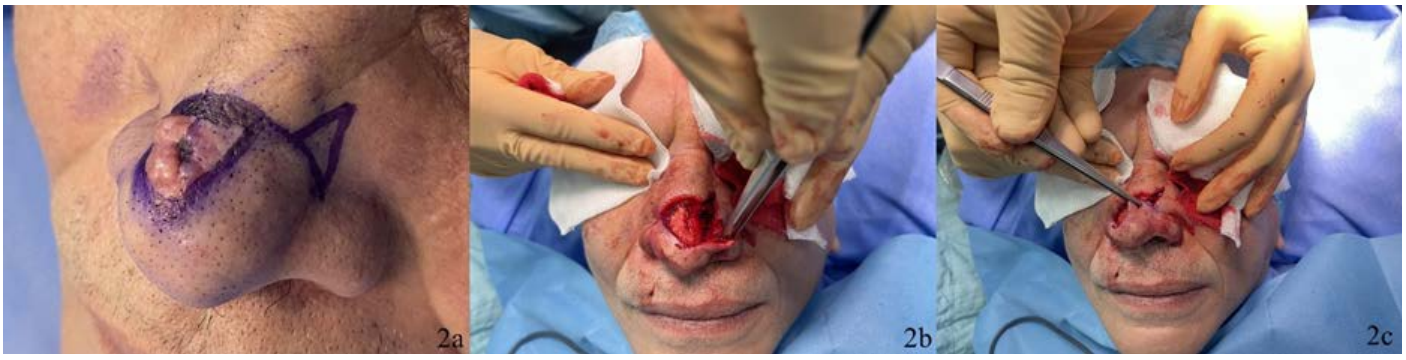

Figure 2a-c. *Intraoperative view: Nasal tip rotation flap: The flap was designed as a medially based superior arc of rotation intended to rotate the entire nasal tip (a). The flap was excised and elevated, followed by undermining of the entire nasal tip just superficial to the perichondrium (b,c).*

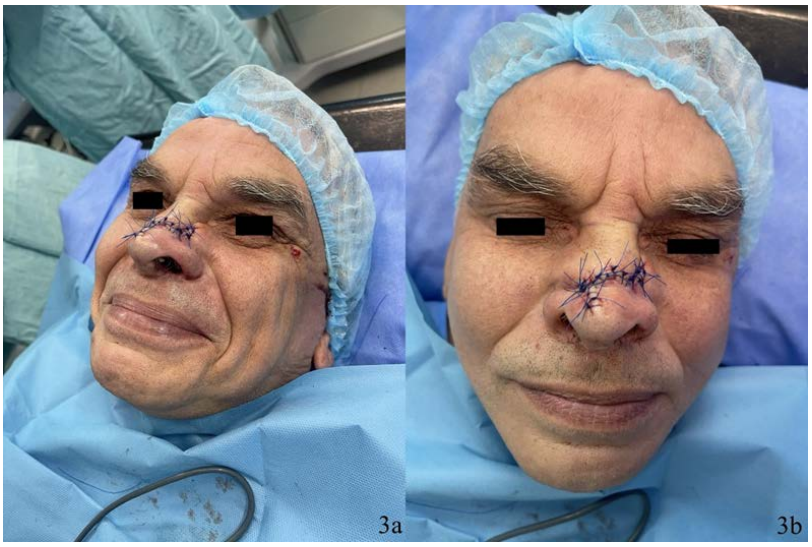

Figure 3. *The secondary defect was closed with single interrupted sutures.*

yet been isolated from foods.

The modern concept of nitroso-photocarcinogenesis involves the deposition of these non-metabolically activated forms of nitrosamines in various tissues, including the skin, where they may undergo photodecomposition under UV irradiation [13]. The subsequent reaction of NO with certain cellular structures may generate mutations responsible for keratinocyte cancers, as well as melanomas [13].

Several important international studies have suggested a potential association between the development of keratinocyte cancers, particularly basal cell carcinoma, and the use of antihypertensive medications [14,15].

In 2017, a study by Nardone et al. [14], the use of ACE inhibitors was associated with an increased risk of non-melanoma skin cancers, including basal cell carcinoma and squamous cell carcinoma, as well as melanoma.

The reported odds ratio (OR) for basal cell carcinoma among ACE inhibitor users was 2.09 (1.87-2.34) in the unadjusted model and 2.23 (1.78-2.81) after adjustment, ARBs (sartans) users was 2.16(1.85-2.52) in the unadjusted model and 2.86 (2.13-3.83) after adjustment, and in the thiazide users was 1.73 (1.49-2.02) in the unadjusted model and 2.11 (1.60-2.79) after adjustment [14].

When comparing the three antihypertensive classes mentioned in the article - ACE inhibitors, angiotensin II receptor blockers (ARBs) and thiazide diuretics - ACE inhibitors ranked second in terms increased risk for basal cell carcinoma risk, with ARBs showing the highest and thiazide diuretics demonstrating the lowest relative risk in comparison [14].

The relationship between phototoxicity and drugs such as ACE inhibitors and hydrochlorothiazide may be related to their chemical structure and their potential to participate in nitrosamine formation [15]. All of these drugs contain secondary or tertiary amino groups and have been reported to show a tendency toward phototoxic reactions, although the exact mechanism remains uncertain [15].

A cutaneous phototoxic reaction results from the interaction between a photosensitizing drug and subsequent exposure to UV irradiation, and for certain medications (such as hydrochlorothiazide), long-term follow up is necessary due to the increased risk for melanoma or squamous cell carcinoma at sites of earlier photosensitivity reactions [16]. According to Tao et al. [17], hydrochlorothiazide may exacerbate UVB-induced photosensitivity in normal skin by impairing the DNA damage response. In keratinocytes, hydrochlorothiazide has been shown to promote the transition from G1 to the S phase of the cell cycle and to inhibit the p53 signalling pathway following UV radiation exposure [17].

Phototoxic reactions are dose-dependent, they occur following sun exposure, and are typically localized to UV-exposed areas [18]. More than 300 medications have been reported to possess the potential to induce phototoxic reactions [19]. The underlying mechanism involves the ability of the basic compound or its metabolites to absorb UV radiation - often due to structural features such as unstable double bonds or tricyclic configuration - thereby reaching an excited, high-energy state [19]. The subsequent return to the ground state is associated with the generation of reactive oxygen species (ROS), which can induce direct DNA damage [18-20].

One possible explanation is the concept of dietary nitrosogenesis [21] or dietary nitroso-photocarcinogenesis [22]. According to this thesis, nitrosamines may form endogenously in the stomach under acidic conditions in the presence of nitrite-rich food, independently of nitroso contamination of the pharmaceutical products [22]. The resulting nitroso compounds, after resorption in the human body, may then contribute to phototoxic or photocarcinogenic processes affecting the human keratinocytes / before metabolic activation in the liver [10,11].

The second also important international observation, published in 2024 was conducted in postmenopausal women and again evaluated the association between photosensitizing antihypertensive medications and the subsequent risk of non-melanoma cancer [23]. Specifically, the use of ACE inhibitors (1.09 [1.01-1.18]), and calcium channel blockers (1.13 [1.05-1.22]), was each associated with an increased risk of non-melanoma skin cancer [23]. The risk further increased with the use of multiple antihypertensive medications and with longer treatment duration [23]. Both drug classes contain secondary amino groups.

The role of polymedication, may be associated with increased blood concentrations of certain (nitroso) compounds, mainly due to drug-drug interactions involving inhibition of cytochrome P450 (CYP) enzymes in the liver, which can enhance their systemic bioavailability [24]. In practice, generics of these drugs may exhibit photocarcinogenic potential which may lead to skin carcinogenesis [25].

Perindopril is an orally administered prodrug that undergoes extensive biotransformation after absorption - approximately 62% of the drug is metabolized through a first-pass effect, while about 38% undergoes systemic hydrolysis [26,27]. Perindopril is converted to its active metabolite, perindoprilat, primarily in the liver through non-CYP450 enzymes, specifically via hepatic ester hydrolysis [26,27]. In addition, metabolism also results in the formation of perindoprilat glucuronide [26]. This compound is generated predominantly from perindopril during pre-systemic first pass metabolism [26]. Both perindoprilat and perindoprilat glucuronide contain secondary amine functional groups [26].

Recently, the focus in nitrosogenesis research has shifted toward the concept of endogenous nitrosamine formation, arising from the oral intake of so-called secondary or tertiary amines that are present within the structure of the active pharmaceutical substances [28,29].

Perindopril, and its metabolites, contain a secondary amine [26,27], which makes it susceptible to nitrosation and the potential formation of N-nitroso-perindopril [30].

Drug-induced photosensitivity associated with the use of perindopril/indapamide has been reported following administration of these medications and subsequent exposure to either ultraviolet or visible radiation [31]. Such reactions suggest that the pure generic drugs, or their nitroso compounds, reach the skin in pharmacologically relevant concentrations [32]. Although direct evidence demonstrating substantial cutaneous deposition is limited in the literature, the occurrence of clinically observable skin reactions supports the hypothesis of systemic bioavailability with secondary availability in the

skin and subsequent skin cancer development [32].

Secondary amines can undergo nitrosation under gastric conditions to form N-nitrosamines before metabolic activation, which may enter systemic circulation, subsequently reach the skin and undergo photodecomposition under UV irradiation, releasing NO/ROS and potentially contributing to DNA damage and skin cancer development [33,34]. Nitrosamines are phototoxic, with their phototoxicity considered independent of their carcinogenicity, due to the instability of their nitroso group under UV light [35-37].

In addition, nitrosamines can be formed in vivo when a drug containing amine functional groups is exposed to nitrosating agents - such as dietary nitrites - under acidic gastric conditions prior to hepatic metabolism [38].

Although the concept of endogenous nitrosamine formation has recently gained considerable attention, the potential impact of exogenous exposure through contaminated pharmaceutical products should not be overlooked. According to the FDA, N-nitroso-perindopril is classified under potency category 5, with recommended AI limit of 1500 ng/day [39].

In all likelihood, these calculations by the regulators may be to great extend inadequate and inaccurate, particularly when viewed in light of current clinicopathological correlations reported worldwide [40-43]. This limitations of the regulators tests stems from the fact that carcinogenic potential is primarily evaluated through testing metabolites after metabolic activation in the liver [44], rather than considering products formed via photodecomposition within the skin. This significant gap explains the weaknesses in global regulatory and manufacturing policies.

Based on the aforementioned considerations, Perindopril can be viewed as real carcinogen through the following mechanisms:

1) Exogenous pathway: N-nitrosamines (N-nitroso-perindopril) or other nitroso compounds may be ingested as impurities in the pharmaceutical product. If these compounds reach and accumulate in the skin/ before hepatic activation, subsequent exposure to ultraviolet irradiation may induce photodecomposition leading to the release of nitric oxide (NO), which can interact with reactive oxygen species (ROS), resulting in DNA damage and potentially contributing to the development of skin cancer [33,34].

2) Endogenous pathway: Secondary or tertiary amines present within the drug structure (perindopril or its metabolites) may undergo nitrosation after ingestion. Under gastric conditions, these amine groups can react with dietary nitrites or nitrates to form N-nitroso compounds (N-nitroso-perindopril, for example). Once formed, these compounds may circulate systemically and, upon exposure to ultraviolet radiation in the skin, undergo photodecomposition, generating NO and ROS that promote DNA damage and may facilitate cutaneous carcinogenesis/ before hepatic activation [33,34].

Clinicopathological correlations are also of importance. Perindopril in the context of polymedication, may possibly be related to the development of basal cell carcinoma [45,46], but melanoma as well [47].

Analogously, Amlodipine may also be considered as a potential carcinogen. Amlodipine is a calcium channel blocker that undergoes extensive hepatic metabolism mediated by cytochrome P450 enzymes, primarily CYP3A4 and CYP3A5 [48].

Endogenous nitrosamine formation: Amlodipine contains a secondary amine within its structure [49], making it susceptible to nitrosation reactions in the presence of dietary nitrites under gastric conditions, than underlying photodecomposition after skin deposition prior to hepatic metabolism [33,34]. In addition, amlodipine has been reported to accumulate in cutaneous tissues and can interact with UVA radiation, potentially inducing photochemical reactions [50,51].

Exogenous nitrosamine contamination may arise from active pharmaceutical ingredients, manufacturing processes, direct or indirect cross-contamination from solvents and equipment, as well as chemical degradation during storage [8].

According to the FDA's list of potentially contaminated medications, N-nitroso-amlodipine is classified within potency category 5, with a recommended AI limit of 1500 ng/day [39].

The number of drug product recalls may vary depending on the manufacturers [8]. A product containing Amlodipine-Valsartan (30.7%) was among the most frequently recalled by several pharmaceutical companies [8,52,53].

Reports in the literature suggest a possible link between amlodipine and the observed clinicopathological findings in everyday clinical practice, sometimes involving basal cell carcinomas requiring extensive reconstructive techniques [54,55].

Flecainide is a potent class IC antiarrhythmic agent that undergoes hepatic metabolism through the CYP450 system, primarily via CYP2D6 [56]. The drug exhibits extensive distribution throughout the body, including adipose tissue [57].

Flecainide may also be viewed as a potential carcinogen due to:

1) It contains a secondary amine within its molecular structure, making it susceptible to possible nitrosation reactions [58];

2) Flecainide is also included in lists of medications with potential N-nitroso-flecainide contamination - according to the FDA, this compound falls within potency category 4, with a recommended acceptable intake (AI) limit of 1500 ng/day [39].

International data linking the use of flecainide with the risk of melanoma and non-melanoma skin cancer in Spain and Denmark have been reported [59].

Flecainide use was associated with an increased risk of melanoma (Denmark only) and non-melanoma skin cancer (Denmark and Spain), although without substantial evidence of dose-response relationships [59].

Antiarrhythmics have been linked to exogenously triggered nitrosogenesis and oncopharmacogenesis, particularly in relation to basal cell carcinoma [60].

The reason for endogenous, dietary related nitrosogenesis or so-called nutritional/dietary mediated nitrosogenesis/photo carcinogenesis may explain the potential differences in the frequency of skin tumors observed across different geographical regions.

Apixaban is an oral anticoagulant that is primarily metabolized via CYP3A4 [61]. In the presence of polymedication, apixaban may interact with other concurrently administered medications;

for example, coadministration with amlodipine can increase systemic exposure to apixaban and consequently elevate the risk of bleeding [61].

Apixaban does not contain a classical secondary amine within its molecular structure, however, the synthetic process of apixaban involves several amide bond-forming reactions and the introduction of a pyrazole-linked secondary amine, which can represent a potential risk for nitrosation and nitrosamine formation [62]. Although this remains hypothetical, concurrent metabolic interactions - such as those with amlodipine - may increase apixaban exposure, and if nitrosamine-related impurities are present, their potential systemic distribution could also potentially increase.

Anticoagulants have been previously been linked to high-risk basal cell carcinoma, in particularly in the context of polymedication, where compounds such as N-nitroso-rivaroxaban may act as cofactors or triggers in the metabolic reprogramming of future cancer cell [63]. Reconstruction with a Mustarde rotation flap was required to close the defect - an outcome possibly related to years of polymedication and potential nitrosocontamination within [63]. Three high-risk basal cell carcinomas in the facial area in a stepwise manner in the context of potentially contaminated drug therapy, including ACE inhibitor (Ramipril), a Beta blocker (bisoprolol), an anticoagulant (rivaroxaban), and folic acid [63].

A limitation of this report is the absence of objective biochemical data, such as measured systemic or tissue levels of nitrosamines in the patient. However, accumulating clinicopathological evidence strongly suggest that intake of medications contaminated with nitroso compounds, or those capable of forming endogenous nitrosamines, may be associated with the development of keratinocyte skin tumors, among other malignancies.

These findings are further supported by experimental studies demonstrating the genotoxic and phototoxic effects of nitroso compounds on keratinocytes, as well as melanocytes. Accordingly, it is the responsibility of pharmaceutical manufacturers and regulatory authorities to ensure clear disclosure regarding the presence or absence of nitroso compounds in medicinal products.

Current scientific data indicate that the mere presence of nitroso compounds in peripheral blood or skin does not result in mutagenic effects [64]. However, within the context of photodecomposition, reactive degradation products with procarcinogenic potential - such as nitric oxide - may be generated. These intermediates can initiate molecular pathways leading to DNA damage and carcinogenesis. Therefore, the detection of nitroso compounds in peripheral blood and skin tissue should not be directly compared with carcinogenicity or photocarcinogenicity without consideration of these additional mechanisms.

The nose is a common location for skin cancer, accounting for approximately 14-27% of all cutaneous cancers [65,66]. As the face represents a person's primary aesthetic unit, nasal tumors pose additional challenges when planning defect reconstruction [67]. Reconstructive options for defects in the distal portions of the nose depend on several factors, including the involved nasal subunits, as well as the depth and size of defect. Commonly used techniques include local flaps such as the East-West advancement, bilobed/trilobed transposition, and dorsal nasal rotation flaps [67-70]. In our patient, nasal tip rotation flap was deemed the most suitable for covering the primary defect following excision of the basal cell carcinoma.

Conclusion.

The identification of nitroso forms of drugs in tissues and blood is not relevant and does not fundamentally limit the significance of the presented data, for the following reasons: 1) it has been demonstrated that nitroso forms of drugs in peripheral blood do not exhibit mutagenic effects in standard assays, including the Ames test, , but their degradation products have mutagenic effects [64]; 2) the distribution of certain medications to peripheral tissues is well established for drugs such as apixaban, flecainide, amlodipine, and perindopril. Logically, their nitroso forms are also reaching the peripheral tissues / including skin/, consistent with previously recognized pharmacokinetic behavior prior to the characterization of nitrosation process in these compounds.

It has been proposed that procarcinogenic mediators may be generated following the breakdown of nitroso compounds during photodecomposition, with subsequent release of nitric oxide and interaction with ROS, leading to the generation of mutations. However, this represents only one proposed pathway within a broader framework of photodecomposition- related mechanisms prior to metabolic activation.

It is further argued that current regulatory testing paradigms may not fully incorporate all stages of the pathogenic cascade of nitroso-photocarcinogenesis, including skin deposition prior to metabolic activation, photodecomposition, and the generation of mutations causing skin cancer. As a result, there is an ongoing discussion regarding whether existing carcinogenicity assessment models adequately reflect these proposed multi-step processes in skin cancer development.

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The authors declare no conflict of interest.

Ethics approval statement is not required.

Written informed consent for publication of their details was obtained from the patient.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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