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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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MULTIPLE KERATINOCYTIC CANCERS AFTER ENALAPRIL/LOSARTAN INTAKE: POTENTIAL LINKS TO DRUG MEDIATED NITROSOGENESIS/ CARCINOGENESIS: MELOLABIAL ADVANCED FLAP AND UNDERMINING SURGERY AS OPTIMAL THERAPEUTIC APPROACH

Georgi Tchernev[1,2].

[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.*

Abstract.

According to scientific databases, nitrosogenesis and carcinogenesis have been inextricably linked for decades and are undoubtedly one of the most serious causes of cancer induction (not only skin cancer) known to humankind.

Some of the most potent modifiers of human DNA turn out to be numerous, known since the last century, difficult to classify as carcinogenic potency, yet available for decades as additional, unregulated, often undisclosed ingredients in about (currently) 300 drugs used by at least 5 billion patients worldwide. While this may sound ridiculous, this information turns out to be reality. A reality accompanied by a drastic jump in the incidence of skin cancers (keratinocytic and melanoma) , but also of predicted general cancers, in relation to the year 2040 and disclosed by Globocan.

Starting from the thesis of nitrosogenesis and possible contamination with mutagens, we present a case of a 95-year-old female who developed 13 keratinocytic tumors within the potentially/actually contaminated intake of drugs from the group of ACE inhibitors/Enalapril and Sartans/Losartan.

A correlation was made between the carcinogenic potency of the possible contaminants (according to the 2023 FDA classification) and the number of cancers occurring within that intake follow-up.

The patient was successfully treated surgically with a melolabial flap for the high-risk tumor under the right eyelid and multiple elliptical excisions for the remaining tumors, followed by extension flaps to cover the defects. The role of nitrosogenesis and its relationship to keratinocytic cancers is discussed and analyzed.

Key words. Losartan, Enalapril, Nitrosamines, NDSRIs, FDA, Nitrosogenesis, dermatologic surgery, melolabial advancement flap.

Introduction.

Multiple keratinocytic tumors in the face and neck are rare [1,2]. Usually, their occurrence is associated with fair skin type, history of burns [2], immunosuppressive therapy [3] or some rare syndromes such as Xeroderma pigmentosum [4], Li fraumeni syndrome [4] or Gorlin Goltz syndrome [5] among others.

Modern, although still speculative according to some colleagues, notions concerning the pathogenesis of skin tumors link contact or intake of nitrosamines contaminating mono- or polymedication in polymorbid patients to the development of several types of skin neoplasms, including keratinocytic cancers [6,7]. Their role as a cofactor is in all likelihood due to the permanent, long-term intake of drugs potentially contaminated with nitrosamines or NDSRIs, and the occurrence of multiple keratinocytic tumors during intake has been previously described [6,7]. Once it has emerged that this intake has been regulated by regulatory authorities, it remains a difficult task for the academic community to become convinced itself that the risk of developing cancers after long-term intake of carcinogenesis is real, and this includes the risk of skin cancer.

This article focuses on 1) the use of the ACE inhibitor enalapril and the angiotensin receptor blocker losartan, 2) their potential/ actual contamination with nitrosamines, 3) the comparison of current data with those shared in international retrospective studies over the years, and 4) and their establishment as a cofactor for the development of multiple epithelial tumors in our patient: 5 keratinocytic tumors in the past (3 basal cell carcinomas/ 2 squamous cell carcinomas) and 5 basal cell carcinomas at the time of current hospitalization. In addition, the patient had several other tumours remaining untreated at this time but planned to be removed in the relatively short term.

Case report.

We report the case of a 95-year-old female patient who visited the dermatology and dermatologic surgery outpatient clinic for multiple non-healing wounds on the face and neck area (Figures 1a,1b). There was no familial burden of skin cancer in the family. No history of intense sun exposure and burns in the past.

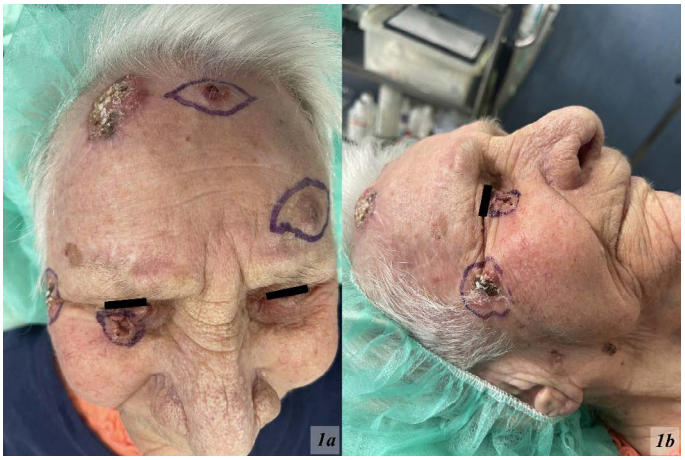

Figure 1. 1a,1b: *Patient with multiple keratinocytic tumors in the head and neck area. Preoperative marking of resection fields.*

The patient had undergone surgery for basal cell carcinoma of the neck in 2009. In 2010, a partial resection of the mandible was performed due to histologically proven differentiated squamous cell carcinoma. In 2014, radiotherapy was performed for histologically proven new basal cell carcinoma of the temporal region. In 2017, a squamous cell carcinoma of the left cervical region was removed, and in 2020, surgical treatment was performed for a basal cell carcinoma of the right temporal region. After 2020, the patient reported growth of multiple analogous lesions that were focally bleeding and causing severe discomfort.

Comordities of the patient included arterial hypertension, type 2 diabetes mellitus, polyneuropathy. As concomitant medication, the following are currently known: enalapril 5 mg twice daily for the period 2005-2014 (9 years); losartan 50 mg half a tablet from 2014 until the time of hospitalization (9 years); benfotiamine 40/ pyridoxine hydrochloride 90/ cinacobalamin 250- 3 times one for several months 18 years ago; pentoxifylline 400 mg twice daily for several months 17 years ago. The dermatological examination revealed (Figures 1a,1b): 1) a round nodular lesion located on the right forehead area, fronto-parietal, measuring 2 x 2 cm, with peripherally raised borders and an uneven, erosive surface, suggestive of basal cell carcinoma; 2) an oval-shaped nodular lesion located on the forehead area centrally, fronto--parietal, measuring 1 x 1 cm, with peripherally raised edges and central erosion;

3) a nodular lesion measuring 1 x by 1 cm, located above the left eyebrow, covered with crusts, suspicious for an epithelial tumor; 4) a right periorbital tumoral lesion measuring 1.3 cm x 1.3 cm, covered with crusts and with a peripheral, slightly raised border, suspicious for basal cell carcinoma; 5) a left preauricular left rounded tumor-shaped lesion measuring 0, 3 cm x 0,5 cm; 6) ulcerated lesion under the right eye, with peripherally raised edges and central crust covered with brownish discharge, suggestive of basal cell carcinoma, and 7) ulcerated tumor-shaped lesion preauricularly on the right, also suggestive of epithelial skin tumor.

Four of the lesions were surgically removed with elliptical excisions (Figures 2a-2c), while the lesion under the right eyelid was surgically removed ovally with near-field resection security, and the defect was covered using a melolabial flap (Figures 3a-3c). Histopathological findings revealed 5 basal cell carcinomas (two nodular, one micronodular and two high-risk infiltrative): 1) nodular basal cell carcinoma under the right lower eyelid with infiltration of one resection line (T1N0M0R1), 2) nodular BCC (T1N0M0) , 3) micronodular basal cell carcinoma (T1N0M0), 4) , and 2 high-risk infiltrative BCC (T1N0M0). Due to infiltration of one surgical margin, active observation, and re-excision if necessary was planned (Figure 4).

The patient was scheduled for surgical treatment in 2 months. She was referred to the regional cancer hospital for registration and further follow-up.

Discussion.

The pathogenesis of skin tumors is quite complex in terms of understanding and interpreting the role of certain extrinsic factors (such as nitrosamines/NDSRIs). Precisely because, according to some colleagues, their current relevance remains

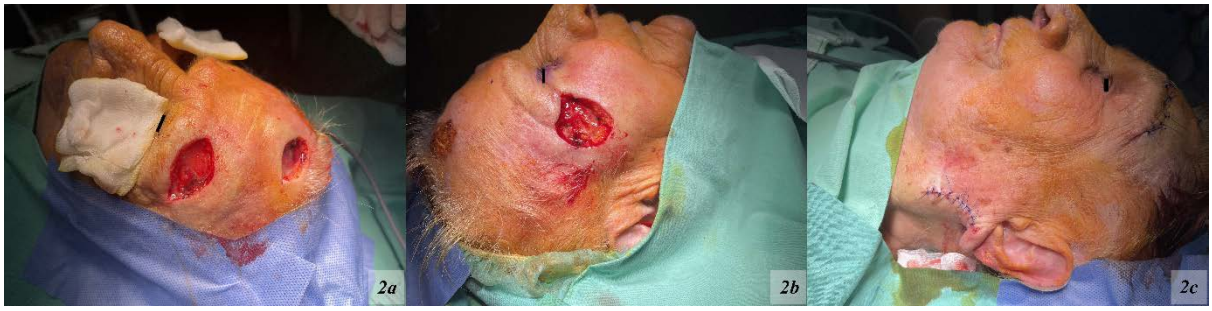

Figure 2. 2a: *Intraoperative aspect after removal of tumors over left eyebrow centrally and frontal area.* ***2b:*** *Intraoperative aspect on the right temporal region.* ***2c:*** *Immediate postoperative findings after closure of defect over left eyebrow and neck area, immediately below left ear.*

Figure 3. 3a: *Second surgical session, intraoperative findings, performing a melolabial flap for a high-risk basal cell carcinoma located adjacent to the right lower eyelid.* ***3b:*** *Melolabial flap with careful dissection of the skin segment prepared for transposition.* ***3c:*** *Melolabial flap prior to definitive fixation of the edges of the segment prepared for transposition.*

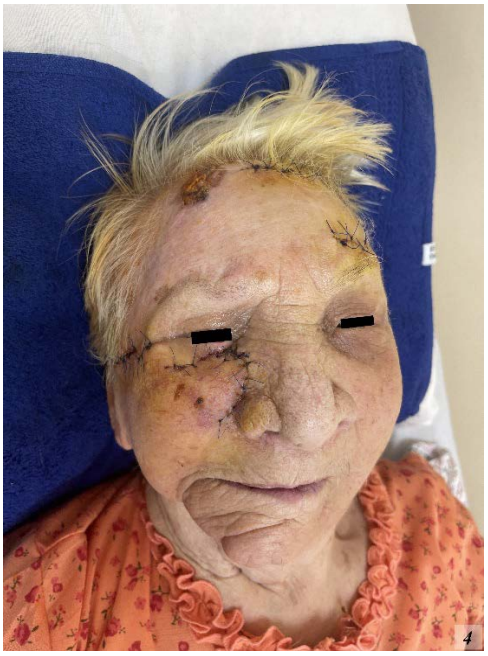

Figure 4. *Melolabial advancement flap on postoperative day 4.*

somewhat controversial and not well understood, rapid and effective solutions regarding prevention are lacking, and this has implications for global health [6,7].

Interestingly, within 9 years of taking enalapril, our patient developed 2 basal cell carcinomas and one squamous cell carcinoma - period 2005-2014.

For the follow-up period (2014-2023), the intake was replaced with losartan for a period of 9 years and the patient developed : 1 squamous cell carcinoma of the neck and 6 basal cell carcinomas in the scalp area, which were operated successfully. There is clinical evidence of at least two additional tumours in the head and neck area.

In practice, the stronger carcinogenic potency of the potential contamination in losartan (1-2) (according to the April 2019 FDA list) could also be related to a two- to threefold risk of keratinocytic tumors, although this thesis is somewhat or according to some colleagues speculative. However, this thesis remains valid at least until regulatory inspections disprove it, which has not happened so far.

A number of international studies in the recent past have linked the use of ACE inhibitors and sartans with the risk of developing keratinocytic tumors [8]: for 1) ACE inhibitors in relation to basal cell carcinomas this risk is elevated more than 200%: adjusted OR (95%CI): 2.23 (1.78-2.81), and in relation to squamous cell carcinomas, the risk is again just under 200% : adjusted OR (95%CI): 1.94 (1.37-2.76) [8].

Regarding sartans, the risk of developing basal cell carcinomas was just below 300% or adjusted OR (95%CI): 2.86 (2.13-3.83), while the risk of developing squamous cell carcinomas was above 200%: adjusted OR (95%CI) of 2.22 (1.37-3.61) [8].

A German collective confirmed these data and also found a significant association between the intake of ACE inhibitors and the development of keratinocytic tumors in the periocular area [9], which presents similarities to the present patient.

However, neither of these two important studies commented on whether the presence of possible carcinogens [8,9], namely nitrosamines, genome modifiers, are the predominant/leading cause of this phenotypic (tumor) manifestation. One of the reasons for this is, therefore, that probably at the time of these studies , the issue regarding nitrosamines was still little known or poorly debated (drug contamination was unknown at that time) [8,9].

But even after its formalization in 2018, the issues continue to be exacerbated to date and despite the problem being globally known, the transparency from checking and declaring peak concentrations of nitrosamines in drugs of a heterogeneous class are categorically lacking/not official to the academic community and end users; despite this lack of full disclosure of the compounds included in the drugs by the pharmaceutical companies, the number of drugs declared as potentially/ hypothetically or actually contaminated is skyrocketing. All these actions or inactions do not diminish the role of nitrosamines as a pathogenetic inducer, but on the contrary, they elevate the importance of its potential role as carcinogens from a high category.

Single publications in the scientific literature associate specifically enalapril and losartan/eprosartan contamination (with nitrosamines) with the development of metatypical basal cell carcinomas in the facial-nasal area and squamous cell carcinomas of the transitional mucosa [10,11]. Enalapril and perindopril administration could also be associated with the occurrence of multiple basal cell carcinomas [12]. These single descriptions are also entirely consistent with previous large-scale international observations from the USA and Germany [8,9].

FDA is in fact the organization that disclosed in 2019 the available possibilities of contamination of sartans, including losartan, with a heterogeneous type of nitrosamines [13].

Again in 2023, the FDA identified a list of potentially nitrosamine-contaminated drugs worldwide (about 270 in number), among which is enalapril [14].

And while according to the official FDA list of contaminated drugs enalapril has a potential carcinogenic potency of 5, losartan has one between 1 and 2 [14].

Whether this higher degree of carcinogenic potency (with potential contamination of losartan) is responsible for the development of significantly more keratinocytic tumors (8 by number) compared with the period of enalapril intake (3 by number) remains unclear, but it is entirely possible and plausible.

Significantly, as already mentioned, these single clinical but consistent observations of ours are confirmed by recent , but also past large retrospective analyses by colleagues in the USA and Germany [8,9]. Their added value is precisely due to the implication of a new possible pathogenetic co-factor: nitrosamines/NDSRIs or so-called genome modifiers [6,7]. A factor that until recently has been left hidden and downplayed to academia, clinicians, and patients due to the the extremely costly implication that this may have for the pharmaceutic industry [15].

The sporadic nature of contamination or the complete absence of any trace of contaminants in a particular class of drugs (in certain geographical regions, in a certain strictly defined time

range) indicates that the absence of contamination could be adequately controlled [16].

In-depth regulatory investigations by FDA and EMA should be seen as one of the most serious steps leading to the discovery of new elements in the pathogenesis of keratinocytic tumors: 1) the presence of nitrosamines in some of the most widely available drugs worldwide - a possible real, present, non-hypothetical inducer of BCC and SCC, but not only.

The prolongation of the technical clarification periods of the manufacturing companies for the problems related to the mono or poly nitrosamine contamination is clearly and absolutely equivalent to the prolongation of the suffering/agony time of the end users - the patients, and this is proven more than conclusively by the worldwide estimated statistics of cancer incidence, but also that of skin cancer [18]: the number of nitrosamine contaminated preparations is growing [13,14], the type of nitrosamines as contaminants is growing [13,14], the predicted cancer incidence (overall) according to globocan by 2040 is growing [17], the incidence of keratinocyte cancers is growing [19,20], as well as that of cutaneous melanoma [21]. The fact that UV radiation prevention is proving to be insufficient or not enough effective suggests, at the very least, that others pathogenetic factors should be implicated, and nitrosamines remain one of the most important candidates for the time being.

Strict FDA and EMA regulatory monitoring should be crucial to limit the availability of contaminants in medicines and achieve precisely the most important target: the safety of millions patients who take the medicines concerned.

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