

GEORGIAN MEDICAL NEWS

ISSN 1512-0112

NO 2 (335) Февраль 2023

ТБИЛИСИ - NEW YORK



ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии
საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНТИ 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 ВИНТИ 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. Корректур авторам не высылаются, 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 computer-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 საქურაღებოლ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დაიცვათ 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 შედეგის 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 ფხიხლებში 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.

Ahmad Ali Alrasheedi. THE PREVALENCE OF COVID-19 IN THE COUNTRIES OF THE GULF COOPERATION COUNCIL: AN EXAMINATION AFTER THREE YEARS.....	6-12
Kordeva S, Cardoso JC, Tchernev G. MULTIFOCAL FIXED DRUG ERUPTION MIMICKING ACQUIRED DERMAL MELANOCYTOSIS.....	13-16
Oksana Matsyura, Lesya Besh, Zoryana Slyuzar, Olena Borysiuk, Olesia Besh, Taras Gutor. ARTIFICIAL VENTILATION OF THE LUNGS IN THE NEONATAL PERIOD: LONG-TERM OUTCOMES.....	17-21
Tchernev G, Kordeva S, Lozev I. METATYPICAL BCCS OF THE NOSE TREATED SUCCESSFULLY VIA BILOBED TRANSPOSITION FLAP: NITROSAMINES IN ACES (ENALAPRIL), ARBS (LOSARTAN) AS POSSIBLE SKIN CANCER KEY TRIGGERING FACTOR.....	22-25
Zahraa M Alzubaidi, Wafaa M. A. Al-attar. NURSES' KNOWLEDGE ABOUT HEPATITIS C VIRUS IN BAGHDAD TEACHING HOSPITALS: A CROSS-SECTIONAL STUDY.....	26-31
Theresa Semmelmann, Alexander Schuh, Horst Rottmann, Reinhard Schröder, Christopher Fleischmann, Stefan Sesselmann. HOW TO AVOID FRACTURE OF THE LOCKING SCREW IN MODULAR REVISION ARTHROPLASTY OF THE HIP USING THE MRP TITAN REVISION SYSTEM.....	32-35
Siranush Mkrtychyan, Razmik Dunamalyan, Ganna Sakanyan, Hasmik Varuzhanyan, Sona Hambardzumyan, Marine Mardiyan. EFFECT OF CHRONIC PERIODONTITIS ON HEALTH-RELATED QUALITY OF LIFE AND ANXIETY AMONG PATIENTS IN YEREVAN, ARMENIA.....	36-40
Raghad O Aldabbagh, Marwah abdulmelik Alshorbaji, Yahya Mohammed Alsabbagh. THE PHYSICAL AND PSYCHOLOGICAL EFFECTS OF MOBILE GAMES ON CHILDREN IN MOSUL/IRAQ.....	41-45
Bukia N.G., Butskhrikidze M.P., Machavariani L.P., Svanidze M.J., Nozadze T.N. ELECTRIC-MAGNETIC STIMULATION PREVENTS STRESS-INDUCED DETERIORATION OF SPATIAL MEMORY.....	46-53
Marko Kozyk, Adam Wahl, Kateryna Strubchevska, Kolosova Iryna, Shatorna Vira. CHRONIC EFFECTS OF CADMIUM CHLORIDE ON RAT EMBRYOGENESIS.....	54-59
Labeeb H. Alsadoon, Kassim Salih Abdullah. COMPARATIVE EFFECT OF INSULIN, GLIMEPIRIDE, AND METFORMIN ON INFLAMMATORY MARKERS IN TYPE 2 DIABETES MELLITUS.....	60-63
Miloslav Doul, Philipp Koehl, Marcel Betsch, Stefan Sesselmann, Alexander Schuh. RETURN TO SPORT AFTER SURGICAL TREATED TIBIAL PLATEAU FRACTURES.....	64-68
Zaid Saaduldeen Khudhur, Uday Hani Mohammad, Nooman Hadi Saeed. HAEMATOSPERMIA: CAUSES AND ASSOCIATED CHANGES IN SEMEN ANALYSIS IN NORTH OF IRAQ.....	69-72
Prots H, Rozhko M, Paliichuk I, Nychyporchuk H, Prots I. STUDY OF BONE RESORPTION AS A RISK FACTOR IN DENTAL IMPLANTATION IN PATIENTS WITH GENERALIZED PERIODONTITIS.....	73-78
Teimuraz Lezhava, Tinatin Jokhadze, Jamlet Monaselidze, Tamar Buadze, Maia Gaiozishvili, Tamar Sigua, Inga Khujadze, Ketevan Gogidze, Nano Mikaia, Nino Chigvinadze. EPIGENETIC MODIFICATION UNDER THE INFLUENCE OF PEPTIDE BIOREGULATORS ON THE "OLD" CHROMATIN.....	79-83
Mudrenko I.G., Kolenko O.I., Kiptenko L.I., Lychko V.S., Sotnikov D.D., Yurchenko O.P. THE PROGRAM OF THE COMPLEX DIFFERENTIATED MEDICAL AND PSYCHOLOGICAL REHABILITATION OF THE PATIENTS WITH SUICIDAL BEHAVIOUR IN DEMENTIA.....	84-89
Tchernev G, Kordeva S. MULTIPLE BCCS AND DYSPLASTIC NEVI AFTER ACE INHIBITORS (ENALAPRIL/PERINDOPRIL): THE ROLE OF NITROSAMINE CONTAMINATION/AVAILABILITY AS SUBSTANTIAL SKIN CANCER TRIGGERING FACTOR.....	90-94
Lyazzat T. Yeraliyeva, Assiya M. Issayeva. CHANGES IN DEATH RATES FROM LOWER RESPIRATORY INFECTIONS BETWEEN 1991 AND 2019 IN THE REPUBLIC OF KAZAKHSTAN.....	95-98
Rocco De Vitis, Marco Passiatore, Giovanni Barchetti, Isabella Ceravolo, Luigi M. Larocca, Marta Starnoni, Francesco Federico, Federica Castri, Giuseppe Taccardo. PATTERN OF A PRIMARY B-CELL LYMPHOMA IN ULNAR NERVE: INTRANEURAL OR EXTRANEURAL.....	99-103
Bazargaliyev Ye, Makashova M, Kudabayeva Kh, Kosmuratova R. EPIDEMIOLOGY OF GENES ASSOCIATED WITH OBESITY IN ASIAN POPULATION. LITERATURE REVIEW.....	104-110

Samsonia M.D, Kandelaki M.A, Baratashvili N.G, Gvaramia L.G. NEUROPROTECTIVE AND ANTIOXIDANT POTENTIAL OF MONTELUKAST-ACETYLCYSTEINE COMBINATION THERAPY FOR BRAIN PROTECTION IN PATIENTS WITH COVID-19 INDUCED PNEUMONIA.....	111-118
Condé Kaba, Carlos Othon Guelngar, Barry Souleymane Digué, Keita Karinka, Diallo Mamadou Hady, Keita Fatoumata Binta, Cissé Fodé Abass. ALZHEIMER’S DISEASE, AN ASSOCIATION OR A COMPLICATION OF PAGET’S DISEASE? STUDY OF AN OBSERVATION IN GUINEA.....	119-120
Condé Kaba, Keita Karinka, Carlos Othon Guelngar, Diallo Mamadou Hady, Keita Fatoumata Binta, Cissé Fodé Abass. CLINICAL AND IMAGING ASPECTS OF TALAR OSTEOCHONDRITIS: A CASE REPORT FROM GUINEA.....	121-123
Fishchenko Iakiv, Kravchuk Lyudmila, Kormiltsev Volodymyr, Saponenko Andrey, Kozak Roman. THE USE OF RADIOFREQUENCY NEUROABLATION IN THE TREATMENT OF OMALGIA IN PATIENTS WITH SHOULDER JOINT ARTHROSIS.....	124-128
V.V. Talash, I.P. Katerenchuk, Iu.A. Kostrikova, T.I. Yarmola, G.L. Pustovoit, L.A. Tkachenko. TERATOMAL NEOPLASMS OF THE PERICARD: THE PROBLEM AND REALITIES (CLINICAL CASE).....	129-136

METATYPICAL BCCS OF THE NOSE TREATED SUCCESSFULLY VIA BILOBED TRANSPOSITION FLAP: NITROSAMINES IN ACES (ENALAPRIL), ARBS (LOSARTAN) AS POSSIBLE SKIN CANCER KEY TRIGGERING FACTOR

Tchernev G^{1,2}, Kordeva S¹, Lozev P³.

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 Common and Vascular Surgery, Medical Institute of Ministry of Interior, General Skobelev 79, 1606 Sofia, Bulgaria.*

Abstract.

The pathogenesis of keratinocytic skin cancer has been well-studied over the years, with a main focus on the influence of UV radiation and the subsequent changes in the genome regulator p53, which affects the cell cycle and the programmed cell death, apoptosis.

Alarming and relatively new trend is the link between nitrosamines in blood pressure medications (but not only) and the development of both melanocytic and keratinocytic skin tumors. In the recent past, high concentrations (above the so-called daily acceptable intake dose) of nitrosamines in ACE inhibitors and sartans became the reason for some of these medications to be officially withdrawn from the drug market. As of now, and according to the lawsuits filed, contamination with even or just one nitrosamine could be the cause of lawsuits for between 5 to 10 forms of cancer overall.

Single case reports, but also large-scale retrospective international studies, find a connection between the intake of possibly nitrosamine contaminated ACE inhibitors / sartans with the subsequent development of basal cell carcinomas.

The same studies also found a serious risk of developing melanomas and squamous cell carcinomas after taking ACE inhibitors, thiazide diuretics and sartans. This, in turn, leads clinicians to ponder the following dilemma: Is it possible that the key pathogenetic link concerning the development of skin cancer is due to their radically different mechanism of action (ACEs/ ARBs/ Thiazides)?

Or, more likely, in all three antihypertensive drug classes, such as sartans, ACE inhibitors, and thiazide diuretics, there is another cancer-causing contaminant, the so-called nitrosamines?

Systemic intake of potentially nitrosamine-contaminated sartans and ACE inhibitors would logically lead to the generation of relatively uniform skin tumors. Proceeding precisely from this thesis, we present two non-related cases of metatypical basal cell carcinomas in the nasal area, which occurred during the administration of ACE inhibitors / angiotensin receptor blockers and were successfully treated by transpositional reconstructive flap – bilobed flap. Possible contamination with nitrosamines as a pathogenetically significant factor is discussed.

Key words. Enalapril, losartan, skin cancer, bilobed flap, dermatologic surgery.

Introduction.

The number of potentially nitrosamine-contaminated blood pressure medications (but not only) is definitely growing, with a number of experts linking the intake of certain drugs and skin

cancer development [1,2]. It appears that ACE inhibitors and thiazide diuretics could be also affected by this contamination [3].

The question, however, remains open: shouldn't the potential contamination of ACE inhibitors with nitrosamines be considered as a possible triggering factor for not only melanocytic but also for keratinocytic skin tumors?

We report two non-related cases of patients, treated for arterial hypertension with losartan and enalapril, who developed metatypical basal cell carcinomas in the nasal region. Bilobed transposition flap technique was used for the successful tumor eradication in both cases.

Case report 1.

A 56-year-old male reported to the dermatology department with primary complaints of skin formation in the nasal area dating from about 7 months.

The dermatology examination showed a round elevated lesion with a dense consistency, located on the left alar part of the nose, in places with telangiectasias and slight discoloration (Figure 1a). Brain cavernoma surgery was performed in the past. Otherwise, the patient was in a good health condition.

Comorbidities: hepatic steatosis and arterial hypertension for which he takes Felodipine 2.5 mg once in the morning and Losartan potassium 50 mg once in the evening for 2 years.

Routine blood tests were performed. The results were in the normal range except for the cholesterol 8.08 mmol/l (normal range – less than 5.17 mmol/l). An ultrasound of the lymph nodes showed a submandibular lymph node on the right with a diameter of 9.7 mm.

Surgery under local anesthesia with 0.5 cm safety margins in all directions was performed (Figure 1b-e) The lesion was removed with a primary oval excision (Figure 1b). The remaining nasal defect was closed by local transposition flap – bilobed flap (Figure 1c,d). The tissue was then closed by single interrupted sutures (Figure 1e).

Histopathology showed metatypical spino-basocellular carcinoma with superficial bleeding, measuring 10/4 mm with clean resection lines. The patient was staged according to the TNM classification as pT1N0M0.

Postoperative edema was observed and methylprednisolone 20 mg once daily for five days i.v., desloratadine 5 mg once daily for six days and daily dressings with iodacept were prescribed. We observed a visible improvement in the nasal edema, and it was recommended removal of the sutures 10-14 days after the operation (Figure 1f), as well as follow-up at the regional

oncology. The established submandibular lymph node was more likely to be inflammatory enlarged or benign and resolved within the subsequent months when checked again echographically. Changes in the systemic therapy for the arterial hypertension was advised and performed in the cardiology ambulance.



Figure 1a-f. First surgical case.

1a: Round elevated lesion with a dense consistency, located on the left ala of the nose, in places with telangiectasias and slight discoloration (a)

1b: Intraoperative finding: The lesion was removed with an elliptical excision.

1c,d: Intraoperative finding: Bilobed flap used for the closure of the remaining nasal defect.

1e: Intraoperative finding: The tissue was closed by single interrupted sutures.

1f: Postoperative finding on day 14.

Case report 2.

A 76-year-old male reported to the dermatology department with primary complaints of skin “wound” in the nasal area dating from 2-3 years. The patient reported that the formation was occasionally bleeding and gradually growing from about 1 year.

The patient reported several comorbidities: atrial fibrillation and flutter with two pacemaker implantations and a reimplantation of the left and right ventricular leads; rheumatic valvular disease - aortic and mitral valve prosthetics with mechanical prostheses - acenocoumarol according to scheme; pulmonary hypertension; hypertensive heart with congestive heart failure; tricuspid insufficiency; arterial hypertension and dyslipidemia (silymarin 90 mg twice a day). A recent surgery for squamous cell carcinoma in the left temporal region was also reported. No family history for malignancy. Allergy to Penicillin.

Systemic therapy for the arterial hypertension: enalapril maleate 10 mg twice a day for 15 years and torsemide 10 mg once a day.

The dermatological examination showed a tumor formation with unclear, undermined borders, covered with hemorrhagic crusts, located on the tip of the nose, slightly on the right nasal area (Figure 2a).

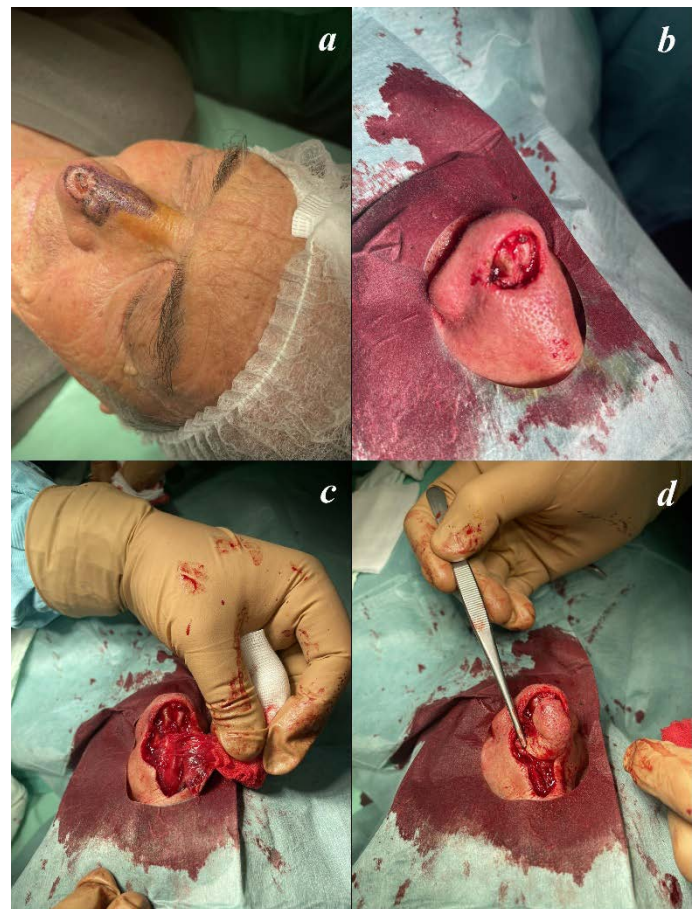


Figure 2a-d. Second surgical case.

2a: The lesion and the further flap reconstruction were preoperatively marked.

2b: Removal of the tumor formation with an elliptical excision.

2c,d: Closure of the remaining nasal defect with bilobed flap.

Routine blood tests were performed. The results were in the normal range except for the platelet count – $96.0 \times 10^9/l$ (normal range $150-400 \times 10^9/l$); the prothrombin time measured two days in a row: INR – 1.35 and 1.51 with normal range 1.1 or below. Enlarged lymph nodes were not observed.

After a consultation with a cardiologist, it was decided to change the acenocoumarol therapy with nadroparin calcium 0.6 ml i.c. twice daily or with heparin 5000 E sc. four times a day. Preoperative biopsy was indicative for metatypical BCC.

Surgical excision of the tumor formation under local anesthesia with lidocaine was recommended. The lesion and the further flap reconstruction were preoperatively marked (Figure 2a). The tumor formation was removed with an oval excision (Figure 2b). Thorough hemostasis was performed, and the remaining nasal defect was closed by bilobed flap (Figure 2c,d). The local transposition flap was closed with single interrupted sutures (Figure 3a). Histopathology confirmed metatypical basal cell carcinoma, staged pT1N0M0, clear resection lines.

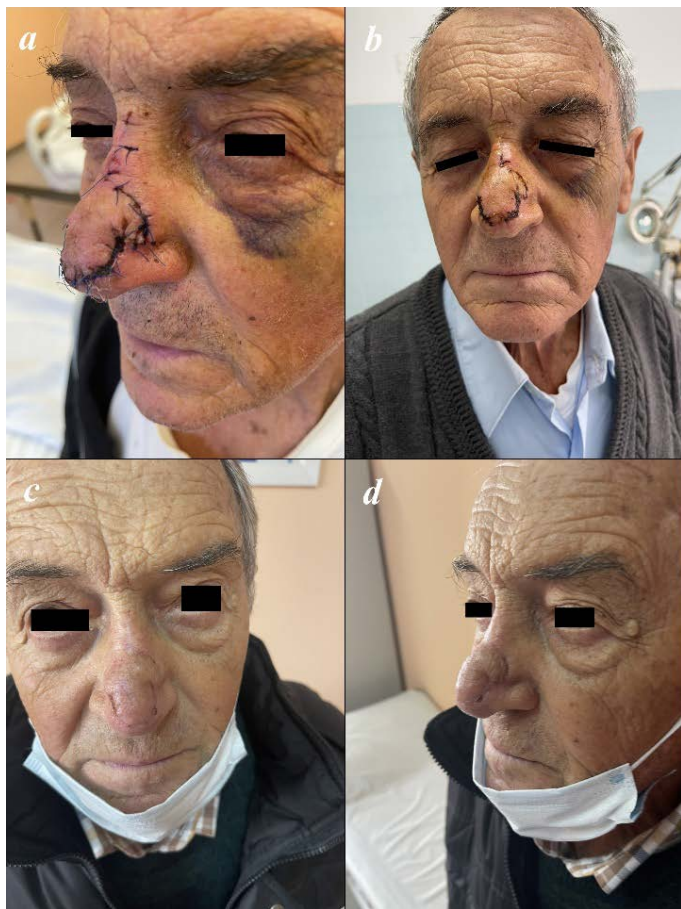


Figure 3a-d. Postoperative findings and significant clinical result.
3a: Closure of the defect with single interrupted sutures.
3b: Postoperative findings after removal of the sutures.
3c,d: Outpatient follow-up 14 days after the operation.

INR examination and consultation with a cardiologist was recommended. Outpatient follow-up and removal of the sutures were performed on days 7 and 10 after surgery (Figure 3b). Significant clinical results were seen 14 days after the operation (Figure 3c,d).

It was recommended that the systemic medication with enalapril maleate 10 mg has to be changed to another one.

Discussion.

Keratinocytic skin tumors, and in particular basal cell carcinomas, have been described as a possible side effect occurring after oral intake of potentially nitrosamine-contaminated sartans (valsartan monotherapy) [4] or sartans in combination with thiazide diuretics (valsartan with hydrochlorothiazide) [5].

Squamous cell carcinomas can also develop after the administration of irbesartan with hydrochlorothiazide (potentially contaminated with nitrosamine) [6], although the number of the described cases in the world literature are currently limited.

Single cases of keratoacanthoma (another type of keratinocyte tumor) were reported after taking irbesartan with hydrochlorothiazide [7].

Although indirect, these factors are in full synchrony with the large-scale retrospective studies of Sable K [8], which associate the use of sartans and ACE inhibitors with an increased risk of basal cell carcinomas: An increased risk for BCC development was determined for sartans (OR: 1,36; 95 CI: 1-1,83) [8], as also for ACEs inhibitors (OR: 1,31; 95 CI: 1,06-1,62) [8].

This relationship is even more significant in the retrospective analysis of Nardone B et al. [9], which associated monomedication with ACE inhibitors with a more than two-fold increased risk for basal cell carcinomas [9]. According to the same publication, the use of sartans as a monomedication in the treatment of arterial hypertension could be associated with a nearly three-fold risk of basal cell carcinomas: (adjusted OR: 2,86; 95 CI: 2,13-3,83) [9].

Losartan, like valsartan, Olmesartan and telmisartan [10-13], is currently more closely related to the development of melanoma and certain melanoma subtypes [14].

Multiple verrucous carcinomas and giant acral melanoma of the heel following Olmesartan and valsartan administration also suggests that potential nitrosamine contamination could be a possible key factor in the development of both keratinocytic and melanocytic cancers (even in single reported cases) [15].

It should be a priority in future skin cancer follow-ups to conduct parallel tests for the detection of nitrosamines, their type and exact concentration in order to clarify their pathogenetic role.

Cutaneous malignancies can sometimes lead to problematic facial defects [16]. In this case scenario the closure of the remaining wound can be quite difficult to manage [16].

Transposition flaps (single-lobed, bilobed and trilobed flaps) are often used in cases when reconstruction is needed [17]. They are extremely useful when the tension in the skin defect is too substantial for primary closure [17].

The bilobed flap is frequently used for facial defects [18]. It was first described by Esser in 1918 in a case of nasal reconstruction, but many authors are using this technique in other anatomical areas when needed [18]. The method provides aesthetically good reconstructive results in closing nasal defects [19] and should be considered by surgeons when primary closure is not sufficient.

Conclusion.

In conclusion, we present two non-related patients with metatypical basal cell carcinomas located on the nasal area, which occurred during the administration of ACEi /ARBs. The patients were successfully treated by transpositional reconstructive flap – bilobed flap. The possible connection between the nitrosamines in the antihypertensive medications and the development of skin cancer is once again discussed.

Funding.

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement.

All authors declare no conflicting interest.

Acknowledgments.

Not applicable.

The patient in this manuscript has given written informed consent for further publication of their case details. The data supporting this study is obtained by the corresponding author.

Research funding.

None declared.

Author contributions.

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests.

Authors state no conflict of interest.

Informed consent.

Informed consent was obtained from all individuals included in this study.

Data availability statement.

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

REFERENCES

1. Tchernev G, Kordeva S, Marinov V, et al. Nitrosamines in antihypertensives, metformin and ranitidine as cofactors for melanoma and development of other cancers. Expert group opinion. *Port J Dermatol and Venereol.* 2022;80:332-334.
2. Tchernev G, Kordeva S, Patterson JW. Nitrosamines and skin cancer: rather reality than a myth? *J Med Review (Bulgarian).* 2023;59:5-7.
3. <https://www.pfizer.com/news/press-release/press-release-detail/pfizer-voluntary-nationwide-recall-lots-accureticm>, 21.03.22.
4. Tchernev G, Oliveira N, Kandathil LJ, et al. Valsartan (and/or Nitrosamine) induced BCC and dysplastic nevi: Current Insights. *Clin Res Dermatol Open Access.* 2021;8:1-6.
5. Malev V, Tchernev G. Dysplastic nevus, and BCC development after antihypertensive therapy with Valsartan and Hydrochlorothiazide?! *Clin Res Dermatol Open Access.* 2019;6:1-2.
6. Tchernev G, Kordeva S, Batashki I, et al. SCC development after Irbesartan/ Hydrochlorothiazide: potential role of Nitrosamines as skin cancer triggering factors. *J Med Review (Bulgarian).* 2023;59:12-14.
7. Tchernev G, Oliveira N, Kandathil LG, et al. Adverse drug reactions: Keratoacanthoma development after systemic administration with Irbesartan/ Hydrochlorothiazide. *J Med Review (Bulgarian).* 2023;58:47-50.
8. Sable K, Majewski S, Nardone B, et al. Association of melanoma and nonmelanoma skin cancer with antihypertensive drugs. A report from the Research on Adverse Drug Events and Reports Project. *J Am Acad Dermatol.* 2016;74:AB221.
9. 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.
10. Tchernev G, Kandathil LG, Oliveira N. Insights into the development of lentigo maligna and dysplastic nevi: spotlight on the possible relation with sartans, thiazides and nitrosamines. *Port J Dermatol and Venereol.* 2022;80:235-240.
11. Tchernev G, Bitolska A, Patterson JW. Telmisartan (and/or nitrosamine) - induced occult melanoma: first reported case in world literature. *Expert Rev Clin Pharmacol.* 2021;14:1075-1080.
12. Tchernev G, Temelkova I. Olmesartan/valsartan induced giant achromatic cutaneous melanoma: "modified" one-step surgical approach with favourable outcome. *J Biol Regul Homeost Agents.* 2019;33:1775-1777.
13. Tchernev G, Temelkova I. Valsartan Induced Melanoma?! First Description in Medical Literature! Open Access Maced J Med Sci. 2018;6:2378-2380.
14. Tchernev G, Oliveira N, Kandathil LJ, et al. Nitrosamine (and/or Losartan/ Hydrochlorothiazide) induced pretibial located Lentigo Maligna: First reported case in the World literature. *Clin Res Dermatol Open Access.* 2021;8:1-3.
15. Tchernev G, Poterov G, Patterson JW, et al. Sartans and cancer: Multiple verrucous carcinomas and giant acral melanoma after antihypertensive therapy with valsartan and Olmesartan. *J Med Review (Bulgarian).* 2020;56:58-60.
16. Starkman SJ, Williams CT, Sherris DA. Flap Basics I: Rotation and Transposition Flaps. *Facial Plast Surg Clin North Am.* 2017;25:313-321.
17. Miller CJ. Design principles for transposition flaps: the rhombic (single-lobed), bilobed, and trilobed flaps. *Dermatol Surg.* 2014;40:S43-52.
18. Dvořák Z, Vavrek V, Kubek T, et al. Bilobed flap in facial reconstruction. *Acta Chir Plast.* 2020;61:10-15.
19. Engell-Nørregård L, Sørensen J. Den bilobulaere lap [The bilobed flap: reconstruction of nasal and extra-nasal skin defect]. *Ugeskr Laeger.* 2007;169:4337-4340.