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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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POLYPHARMACY, DRUG RELATED NITROSAMINE CONTAMINATION (BISOPROLOL/ PROPAFENONE) AND THE LINK TO LICHEN PLANUS/ SUBSEQUENT DEVELOPMENT OF KERATINOCYTE AND MUCOSAL CANCER/ ORAL LEUKOPLAKIA: PRESENTATION OF THE FIRST CASE AND UPDATE ON THE NEW PATHOGENETIC VISION

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Abstract.

The association between drug-induced lichen planus – whether oral/mucosal or solely cutaneous – involves a diverse range of drugs, including ACE inhibitors, diuretics, and beta blockers, as well as quinidine, NSAIDs, hydroxychloroquine, antiretroviral medications for HIV, penicillamine, TNF inhibitors, and certain medications for type 2 diabetes. The natural course of lichen planus has been also linked in certain cases to the development of squamous cell carcinoma, affecting both mucous membranes and skin, as extensively documented in the literature. However, little attention has been given to the fact that many of the medications associated with lichen planus – such as ACE inhibitors, diuretics, and beta blockers – are listed by the FDA as contaminated with carcinogenic and mutagenic nitrosamines. These compounds exhibit photocarcinogenic, carcinogenic and mutagenic properties. Their potential role in the progression of lichenoid lesions to oral leukoplakia, oral carcinomas and squamous cell carcinoma, but also strictly cutaneous located tumour has not been previously explored, yet it appears both plausible and significant.

We present for the first time in the medical literature, a case of a 91-year-old patient with a 2-year history of oral lichen planus and subsequent oral leukoplakia following 2-year beta-blocker (bisoprolol) and/or anti-arrhythmic (propafenone) administration, with no history of smoking and alcohol consumption, and discuss the possible role of nitrosamines as a cofactor in the malignant transformation of ulcerative lichenoid lesions to oral leukoplakia/ mucosal carcinoma.

The adverse effects of these medications may be categorized into those related to 1) the active substance – potentially triggering lichen planus and those 2) linked to contaminants/ carcinogens/ mutagens, such as nitrosamines, which may act as primary or contributory factors in skin carcinogenesis in direction development of oral leukoplakia and oral/ cutaneous carcinomas.

Key words. Lichen planus, oral leukoplakia, squamous cell carcinoma, beta blockers, bisoprolol, nitrosamines, photocarcinogenic, carcinogenic, propafenone.

Introduction.

Lichen planus (LP) is a chronic immune-mediated inflammatory disease, affecting both the skin and mucous membranes, with the buccal mucosa being the most frequently involved oral site [1]. The disease is estimated to affect 1-2% of the general population, with a higher prevalence in women compared to men [2]. It can manifest in various forms, such as plaque-like, reticular, papular, erosive, atrophic or bullous types [2]. The oral lesions may occur independently or alongside other cutaneous lesions [2].

Two primary pathogenetic inflammatory mechanisms are suggested to be part of the development of the oral lichen planus [3]. The antigen-specific pathway involves antigen presentation by basal keratinocytes and antigen-specific keratinocyte destruction by CD8(+) cytotoxic T-cells [3]. The non-specific pathway involves mast cell degranulation and matrix metalloproteinase activation within the lesions [3]. Some authors suggest that a "combined" pathway involving both mechanisms leads to T-cell accumulation in the superficial lamina propria, basement membrane alteration, intraepithelial T-cell migration, and keratinocyte apoptosis [3].

The activation of nuclear factor kappa B (NF-kB) and the inhibition of the transforming growth factor control pathway (TGF-beta/Smad) promote hyperkeratosis and the development of characteristic white lesions, contributing to the chronic progression of oral lichen planus (OLP) [4].

Several trigger factors have been associated with the development of lichen planus, including infectious agents such as hepatitis C virus [5], the COVID-19 virus and vaccine [6] certain metal compounds used in dental restorations, such as mercury, copper, and gold, as well as certain medications like angiotensin-converting enzyme inhibitors, beta blockers, thiazide diuretics, quinidine, nonsteroidal anti-inflammatory drugs, antimalarials (hydroxychloroquine), antiretroviral medications for HIV infection, penicillamine, tumor necrosis factor-alpha inhibitors, oral hypoglycemic medications for type 2 diabetes, and gold salts [5,7-9].

According to some colleagues, chronic cutaneous inflammatory lesions can induce an oncogenic-like overactivation of growth factors, stimulating epithelial cells toward malignant transformation [10].

In contrast, whereas oral lichen planus is considered a premalignant lesion, cutaneous lichen planus has little to no established connection with squamous cell carcinoma [10]. The development of squamous cell carcinoma in cutaneous lichen planus has an incidence of 0.4%, with the hypertrophic type being the most commonly implicated subtype [10-12].

It is suggested that the inflammatory effects on basal keratinocytes in oral lichen planus may contribute to carcinogenesis [13].

Interestingly, oral lichen planus and both early and advanced oral squamous cell carcinoma share common pathways, with

key tumor suppressors and oncogenes associated with different immune processes being dysregulated in oral lichen planus [13].

When orally administered drugs contain carcinogenic compounds such as nitrosamines, we share the thesis, that the active substance may contribute to the development of lichen planus, while potential/actual contaminants serve as possible cofactors in the progression of these lesions to neoplastic changes, including leukoplakia and/or squamous cell carcinoma.

More recent evidence connects lichen planus to both cutaneous and mucous carcinomas, with some considering it a precursor lesion to squamous cell carcinoma, though the exact mechanisms remain somewhat unclear [10-14].

New horizons include identifying entirely new triggers or potential triggers for skin neoplasms, such as squamous cell carcinoma. For example, certain medications prescribed for various conditions – most commonly arterial hypertension – have been found to contain nitrosamines, which may contribute to carcinogenesis.

We report a case of a 91-year-old male with a 2-year history of oral lichen planus and oral leukoplakia following the initiation of systemic treatment with bisoprolol and propafenone, with no history of smoking or alcohol consumption. The potential novel mechanisms of disease pathogenesis are explored in the context of drug-induced nitrosogenesis, nitroso carcinogenesis, and oncopharmacogenesis, specifically regarding the probability of bisoprolol- and/or propafenone-induced oral lichen planus, its progression to leukoplakia, and the subsequent possible risk of developing squamous cell carcinoma. The role of nitroso contamination as a possible cofactor in the development of precursor lesions for oral carcinoma is also discussed, based on their genotoxicity.

Case report.

A 91-year-old male presented with primary complaints of changes in the tongue's and buccal mucosa, both persisting for approximately two years. The tongue changes were characterized by painful sores with a whitish plaque.

The patient has a history of choledochectomy in early adulthood and appendectomy in childhood. In 2023, he developed COVID-19-associated bilateral bronchopneumonia. His chronic conditions include arterial hypertension, benign prostatic hyperplasia, and atrial fibrillation with flutter. Additionally, he has a known allergy to formaldehyde. The patient neither smoked nor consumed alcohol and was actively involved in sports during his early years.

He had been on systemic therapy since 2023, including apixaban 2.5 mg twice daily – once in the morning and once in the evening, bisoprolol fumarate 2.5 mg once daily in the morning, propafenone hydrochloride 300 mg half a tablet three times a day, and spironolactone 25 mg once in the morning.

The dermatological examination revealed fine, band-shaped, slightly raised gray-whitish plaques on the buccal mucosa, characteristic of Wickham's striae, positioned above the surrounding mucosa and tending to merge into a network-like pattern (Figure 1a). Additionally, single erosions and erythematous papular changes were observed on the tongue, accompanied by papillary loss and whitish plaque covering the affected areas (Figure 1b,c). Enlarged lymph nodes were not palpable.

Routine blood tests revealed no abnormalities except for hemoglobin – 134.0 g/L (normal range for men 138.0-172.0 g/L), hematocrit – 0.387 L/L (normal range 0.41-0.50 L/L), HDL – 1.0 mmol/L (normal range: >1,6 mmol /l) and CRP – 6.6 mg/L (normal range less than 3.0 mg/L).

Due to the erosive changes affecting the tongue and buccal mucosa, the differential diagnosis included erosive lichen planus, squamous cell carcinoma, pemphigus vulgaris, and lichen planus. To aid in diagnosis, direct immunofluorescence testing and two biopsies were performed. The result of the direct immunofluorescence test was inconclusive, and a second test was recommended.

The first biopsy, taken from a whitish reticular enanthem on the buccal mucosa, revealed abundant parakeratosis, patchy acanthosis, and vacuolar degeneration of the basal keratinocyte layer, with obscuration of the dermo-epidermal border by a lichenoid lymphoplasmacytic inflammatory infiltrate lining the tunica propria. The histological findings were consistent with lichen planus (Figure 2a,b).

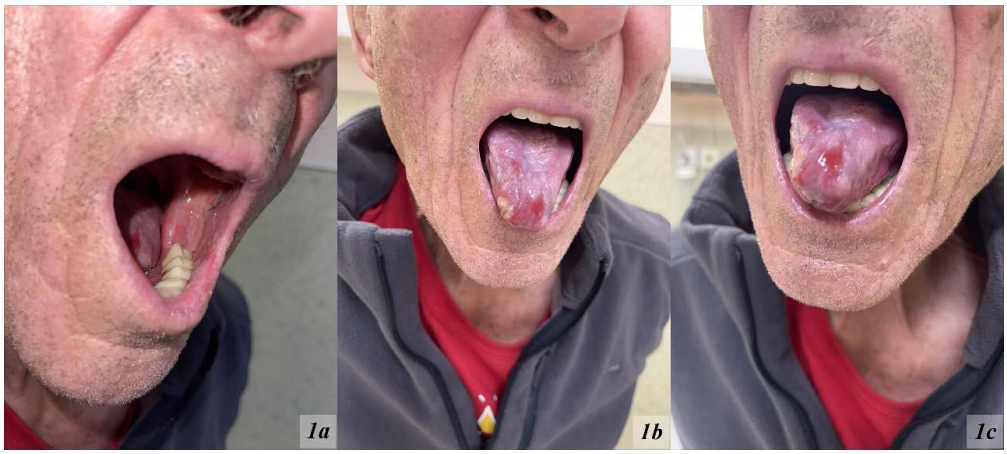

Figure 1a-c. 1a: *Fine, band-shaped, slightly raised gray-whitish plaques on the buccal mucosa, characteristic of Wickham's striae, positioned above the surrounding mucosa and with tendency to merge into a network-like pattern.*
1b,c: *Single erosions and erythematous popular changes on the tongue, accompanied by papillary loss and whitish plaque covering the affected areas.*

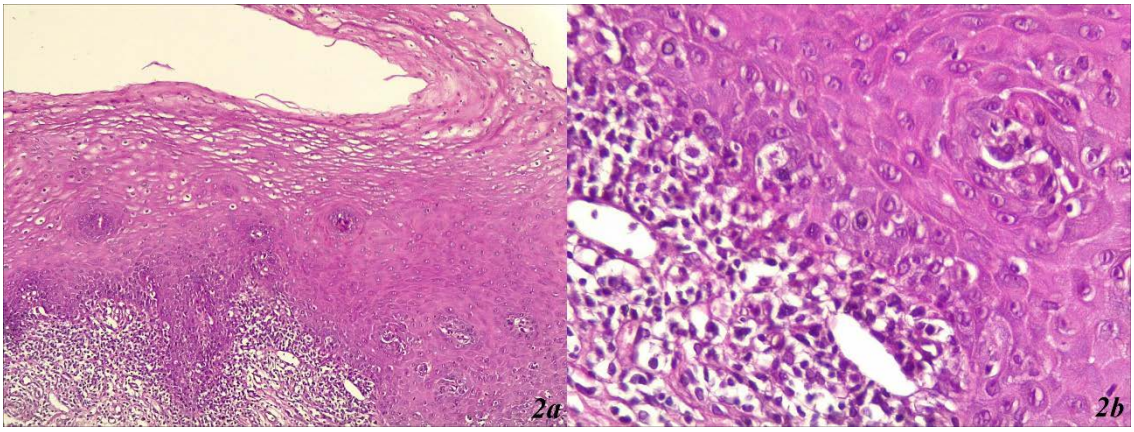

Figure 2a,b. *Histology panel lichen planus: abundant parakeratosis, patchy acanthosis, and vacuolar degeneration of the basal keratinocyte layer, with obscuration of the dermo-epidermal border by a lichenoid lymphoplasmacytic inflammatory infiltrate lining the tunica propria.*
2a: *lichen planus x HE x 100.*
2b: *vacuolar degeneration of the basal cell layer x HE x 200.*

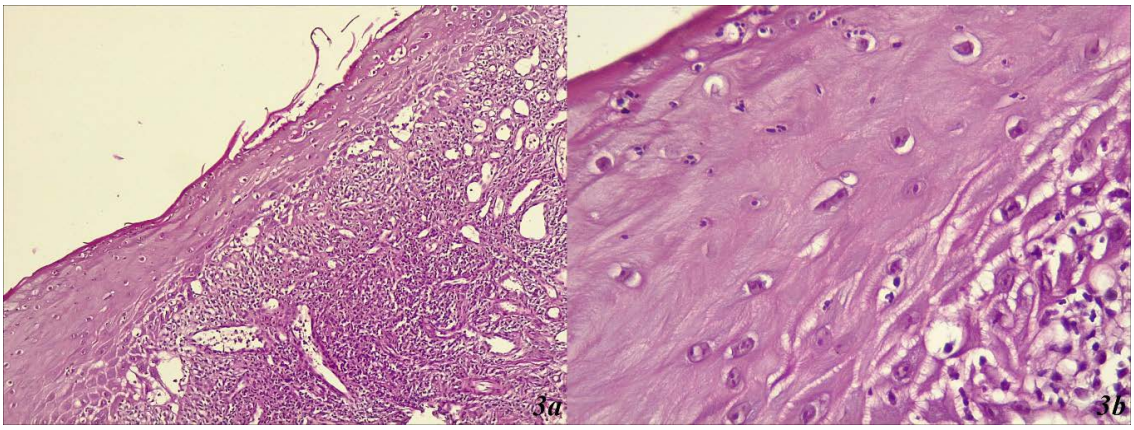

Figure 3a,b. *Histology panel leukoplakia: orthohyperkeratosis with filiform and oval hematoxylin-stained inclusions, patchy acanthosis with dyskeratosis, binucleated keratinocytes, and disrupted epithelial architecture throughout the epithelial segment. The segment is demarcated by an abundant lichenoid round-cell stroma, prominent among collagen fibers throughout the tunica propria.*
3a: *Full thickness intraepithelial dysplasia x HE x 100.*
3b: *Dyskeratotic cells and irregular keratinocytic arrangement x HE x 200.*

The second biopsy, taken from an erythematous-infiltrative plaque with an erosive surface on the tongue, revealed orthohyperkeratosis with filiform and oval hematoxylin-stained inclusions, patchy acanthosis with dyskeratosis, binucleated keratinocytes, and disrupted epithelial architecture throughout the epithelial segment. The segment was demarcated by an abundant lichenoid round-cell stroma, prominent among collagen fibers throughout the tunica propria. The histological findings are consistent with oral/ tongue leukoplakia (Figure 3a,b).

The patient was prescribed methylprednisolone 4 mg following a tapered regimen: week 1 - two tablets in the morning and one in the afternoon; week 2 – two tablets in the morning and half a tablet in the afternoon; week 3 - one tablet in the morning and one in the evening; and week 4 – one tablet in the morning and half a tablet in the afternoon. Additionally, he was started on acitretin 25 mg once daily in the morning for an initial period of one month, followed by a control examination. Topical calcipotriol/ betamethasone gel was prescribed twice daily, along with chlorhexidine digluconate solution to be swallowed three times a day before meals. Other medications included famotidine 40 mg once in the morning and once in the afternoon, apixaban 2.5 mg once in the morning and once in the evening. Bisoprolol fumarate was replaced with moxonidine 0.2 mg once daily in the morning.

Discussion.

The association between lichen planus and skin cancer remains somewhat unclear [12]. According to some authors, the chronic inflammatory environment associated with lichen planus can lead to genetic alterations and impair cell cycle regulation, thereby increasing the risk for cancer formation [11,12]. Some forms of lichen planus, such as the hypertrophic lichen planus, have been documented in the literature as a potential precursor lesions for squamous cell carcinoma [12], characterized by highly aggressive and invasive nature, along with a tendency for widespread metastasis [15]. Although fewer than 50 cases have been reported in the literature regarding hypertrophic lichen planus and squamous cell carcinoma development, fatal outcomes can occur [15].

No one to date in the literature has looked for an explanation as to whether drug-induced forms of lichen planus that progress

to oral or cutaneous carcinomas are accompanied by the intake of nitrosamine-contaminated medication.

Cutaneous squamous cell carcinomas are known in the literature to be associated with certain risk factors, including radiation exposure, ultraviolet rays, burn scars, varicose ulcers, human papilloma virus, chronic tar application, arsenic exposure [16,17], as well as chronic irritation from itching, areas of depigmentation in lichen planus lesions, and long-standing non-healing lichen planus lesions [10].

The correlation between oral lichen planus and malignant transformation is even more pronounced in terms of potential to progress to oral squamous cell carcinoma [14]. Oral lichen planus on its own is not cancerous, but it can elevate the chances of developing oral cancer [18]. To assess the risk of malignant transformation in lichen planus, Sigurgeirsson et al. [19] conducted a study following 2071 patients with lichen planus for an average of 9.9 years. The findings demonstrated a significant increase for oral cancer among male subjects, with a morbidity ratio of 5.9 (95% confidence interval, 2.5 to 11.4) [19]. Interestingly, patients whose oral cancer developed from oral lichen planus exhibited slightly better survival rates – 82% of OLP cases versus 77% of non-OLP cases - compared to those without a prior history of oral lichen planus [18].

A cohort study by Halonen et al. [20] studied 13,100 women in Finland diagnosed with lichen planus and subsequent cancer diagnosis. The results showed 1520 women with lichen planus were later diagnosed with cancer (SIR 1.15, 95% confidence interval [CI] 1.09-1.20) [20]. The study identified an increased risk for several cancer types, including cancer of the lip (SIR 5.17, 95% CI 3.06-8.16), tongue (SIR 12.4, 95% CI 9.45-16.0), oral cavity (SIR 7.97, 95% CI 6.79-9.24), esophagus (SIR 1.95, 95% CI 1.17-3.04), larynx (SIR 3.47, 95% CI 1.13-8.10) and vulva (SIR 1.99, 95% CI 1.18-3.13) [20].

In addition to squamous cell carcinoma, patients with lichen planus may also develop basal cell carcinoma [21]. In terms of pathogenesis, it remains unclear whether malignant transformation is merely a coincidence or co-localization, or if additional triggering factors are involved beyond our current knowledge [21]. Nevertheless, a history of chronic sun exposure (UVB), facial location, and the persistence of a lesion at the same site over an extended period can be considered at least cofactors in basal cell carcinoma transformation [21]. This event is exceptionally rare [21], with only a single documented case of lichen planus progressing to basal cell carcinoma, suggesting that additional external factors/compounds may play a role in initiating the malignant transformation.

Nitrosamines in patients' medications seem to be a strong candidate as a potential cofactor in skin carcinogenesis. They are known carcinogens, mutagens and phototoxic substances.

Malignancy in oral types of lichen planus is generally common and is often attributed to various risk factors, including smoking, alcohol consumption, erosive phenotype of the lesion, tongue localization, female gender, and hepatitis C infection [22].

It is noteworthy that factors such as smoking and alcohol consumption are associated with the nitrosogenesis of cancer, primarily through the presence of nitrosamines, which act as modulators of the human genome [23].

Nitrosamines, which are recognized human carcinogens, have been directly linked to the pathogenesis of oral cancer [23].

Their impact extends beyond carcinogenicity, including mutagenicity, embryopathy, and teratogenicity [23].

Tobacco-specific N-nitrosamines (TSNAs), present in tobacco smoke alongside other mutagenic and carcinogenic compounds, function as procarcinogens that require metabolic activation to induce DNA modifications [23]. The chemical compounds found in tobacco products, particularly TSNAs, exhibit not only carcinogenic properties but function as tumor primers, tumor promoters, co-carcinogens, and organ-specific carcinogens [24]. TSNAs can trigger not only oxidative stress and genotoxicity but also oncogenic activation, leading to a subsequent metabolic response [25]. The TSNAs signalling pathways contribute to the reprogramming of energy metabolism and may play a role in the bioenergetic reprogramming of both precancerous and cancerous cells [25].

Smokeless tobacco contains TSNAs, including N-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-butanone (NNK), which upon absorption and metabolism, generate reactive compounds that induce DNA adducts, resulting in alterations in target genes such as RAS oncogenes and the p53 tumor suppressor gene [26]. Although the mechanisms of DNA repair eliminate most adducts, thereby preventing mutations, some remain unrepaired, leading to carcinogenesis [26].

Based on the presented data, it can be concluded or hypothesized that lichen planus may contribute to the development of oral and cutaneous carcinomas, with oral carcinomas being particularly influenced by the presence of nitrosamines in various forms.

Nitrosamines have also been detected in alcoholic beverages during investigations into the association between alcohol consumption and esophageal cancer [27]. N-nitrosodimethylamine (NDMA) was found in most alcoholic beverages, except for wine, while detectable levels of N-nitrosodiethylamine (NDEA) were identified in spirits and ciders [27]. The concentration of nitrosamines in wine was found to be low [28]. The cancer incidence is further amplified in individuals, who both smoke and consume alcohol [28]. A hypothesis was suggested that the ethyl alcohol can inhibit the hepatic metabolism of the nitrosamines, allowing them to circulate to other organs such as the kidneys and esophagus, where they can undergo activation into carcinogenic compounds [28]. Notably, the pattern of DNA damage observed in the patient's cells closely resembles that induced by nitrosamine exposure [28].

Different nitrosamines can also be found in drinking water, including N-nitrosomethylamine (NMEA), N-nitrosodiethylamine (NDEA), N-nitrosodimethylamine (NDMA), N-nitrosodi-n-propylamine (NDPA), N-nitrosopyrrolidine (NPyr), N-nitrosopiperidine (NPip), and N-nitrosodinbutylamine (NDBA) [29]. Interestingly, all seven aforementioned nitrosamine compounds were detected in water samples, with NDMA exhibiting the highest concentration at 10.2 ng/L [29], in contrast, NDMA was present in beer samples at lower concentrations (0.12-0.23 microg/L) [29]. The estimated cancer risk associated with NDMA was 6.4×10^{-6},

while the risk for other nitrosamines remained below 10^{-6} [29].

The available data strongly indicate that nitrosamines, in various forms, contribute to the development of carcinomas of the oral cavity, vulva, pharynx, and esophagus, among others [20]. Notably, the same nitrosamines are present in medications identified as potential inducers of lichen planus, including angiotensin-converting enzyme inhibitors, beta blockers, thiazide diuretics, quinidine, nonsteroidal anti-inflammatory drugs, antimalarials, antiretroviral medications for HIV infection, penicillamine, tumor necrosis factor-alpha inhibitors, oral hypoglycemic medications for type 2 diabetes [5,7-9]. Furthermore, additional medications that have not yet been explicitly described may also contain nitrosamines, raising the possibility that their intake could be associated with the development of oral or cutaneous carcinomas, developing ion lichenoid type of lesions: oral and mucosal.

We report, for the first time in the literature, a consistently observed association between the intake of antihypertensive and antiarrhythmic medications – specifically bisoprolol under potency category of 4 and propafenone under potency category of 2 – both listed by the FDA as potentially contaminated with nitrosamines [30] – and the relatively short-term development of oral leukoplakia. This pathogenetic association reinforces the hypothesis and emerging theory of drug-mediated oncopharmacogenesis or drug-induced carcinogenesis [31,32]. In all likelihood, potential nitrosamine contamination, particularly in the context of polymedication/ polycontamination/ polypharmacy, may serve as a key triggering factor for the development of oral carcinomas and precancerous lesions like the oral leukoplakia.

Oral leukoplakia can arise as a direct progression/evolution of oral lichen planus [33]. In a study conducted by Garcia-Pola et al. [33], 515 oral lichen planus lesions, from which 14 patients (2.7%) developed proliferative verrucous leukoplakia. Three of the patients developed subsequent squamous cell carcinoma, and one – two verrucous carcinomas [33].

The incidence rate for oral leukoplakia in patients with lichen planus is different based on the population [34]. The new oral leukoplakia lesions were found to be located on gingival/alveolar ridge (33.3%) compared to other oral sites, and lichen planus at buccal site (33.3%) [34]. Interestingly, in cases with diabetes mellitus, the relative risk for oral lichen planus was 6.4(95% CI: 2.4-17.6) [34]. The incidence of oral leukoplakia and lichen planus varies; however, both conditions are again associated with external factors such as the tobacco-specific nitrosamines [35]. The highest frequency of leukoplakia was detected in smoking individuals (again connection to nitrosamines), with 66.66% of patients with dysplastic leukoplakias being tobacco users [35].

This raises the possibility that, in patients who neither smoke nor consume alcohol, the development of lichen planus and oral leukoplakia may be attributed to nitrosamine exposure through medications, specifically beta-blockers like bisoprolol and antiarrhythmic drugs like propafenone.

Cutaneous lichenoid drug eruptions (LDE) appear to be significantly underrecognized, despite being uncommon yet not rare [36]. By nature, they are adverse drug reactions that typically resolve upon discontinuation of the drug culprit [36].

A narrative review conducted by Maul et al. [36] analyzed 323 cases with LDE, identifying checkpoint inhibitors as the most frequently implicated drug class, accounting for 136 cases (42.1%) [36].

Tyrosine kinase inhibitors were the second most common with 39 cases (12.0%), followed by anti-TNF-alpha monoclonal antibodies with 13 cases (4.0%) [36]. The median time between drug intake and clinical manifestation was 14.2 weeks (ranging from 0.1 to 208 weeks) [36]. Notably, the longest recorded latency period of 208 weeks equates to 3.986393 years or almost 4 years [37], highlighting the potential delayed onset of LDE following drug exposure.

In our case, oral lichen planus and oral leukoplakia, or their initial manifestations on the buccal mucosa and tongue, appeared simultaneously approximately 2 years ago. Notably, this timeline aligns with the initiation of bisoprolol and propafenone therapy, as indicated by the patient's medical history.

Besides beta-blockers, methyldopa, NSAIDs, antimalarials, penicillamine and sodium aurothiomalate, biologic drugs such as adalimumab, etanercept, infliximab, and dupilumab have also been associated with the development of lichenoid eruptions [38]. Kern et al. [38] reported a case of dupilumab-induced oral and cutaneous lichen planus, suggesting a possible underlying mechanism. This may be attributed to the downregulation of T-helper 2 cell activation via inhibition of the interleukin-4/ interleukin-13 pathway, resulting in a TH1/TH2 imbalance [38]. The shift toward a TH1-mediated immune response may contribute to the pathogenesis of drug-induced lichen planus [38].

Even medications not typically linked with drug-induced reactions of the oral mucosa have been implicated, emphasizing the need for recognition [39].

Allopurinol, a medication not commonly linked to oral reactions, has been reported as a causative agent for oral lichenoid lesions affecting the bilateral buccal mucosa, tongue, and labial mucosa [39].

While drug-induced eruptions generally improve or resolve upon discontinuation of the drug culprit, malignant transformation has been observed in certain cases, underscoring the importance of early and accurate [39].

According to the literature, oral forms of lichen planus are linked to oral leukoplakia, which is recognized as a precursor lesion for oral carcinoma [33]. On the other hand, drug-induced forms of lichen planus are also linked to the use of beta-blockers [40] and antiarrhythmics [41], which are included in the FDA list of nitrosamine-contaminated medications with carcinogenic potential [30].

The recognition and thorough investigation of the above-mentioned associations could significantly aid in identifying specific factors or cofactors with well-established carcinogenic potential.

Eliminating such contaminants from the pharmaceutical market should be a priority. Drug related adverse effects arise from both 1) the active drug substance itself and 2) the presence of carcinogenic contaminants, which together create sometimes a synergistic effect in relation to cancer development and

progression. This explains the dual impact: 1) the development of oral or/and cutaneous lichenoid lesions and 2) the heightened risk of these lesions progressing into precancerous conditions, such as oral leukoplakia, or even directly neoplastic lesions, including carcinomas. The latter is particularly concerning, as it is mediated by genotoxic, phototoxic substances, most notably known as nitrosamines.

The fact that intake of potentially nitrosamine-contaminated drugs such as bisoprolol (in the context of mono- or polymedication), are associated with the development of both keratinocytic cancers [42-46] and melanoma [31,47,48] is indicative of their potentially carcinogenic and phototoxic effects.

Similarly, preliminary clinical observations regarding the intake of potentially nitrosamine-contaminated propafenone have linked it to the development of melanomas [49] as well as to that of epithelial skin tumors [50,51].

Nitrosamines are known photocarcinogens, and their phototoxicity is mainly defined on the decomposition, the instability of their nitroso group under the influence of solar radiation [52- 54].

It should not be surprising to anyone that the intake of two potentially nitrosamine-contaminated drugs (such as bisoprolol and propafenone) could be pathogenetically associated with the occurrence of oral leukoplakia based on erosive lichen planus.

As well as that lesion evolution in cutaneous forms of lichen planus in the context of polycontaminated polymedication could also be a good explanation for the occurrence of cutaneous carcinomas.

A critical observation is that, to date, no pharmaceutical product worldwide has incorporated life-prolonging compounds, such as ginseng for example, into standard formulations.

Yet, multiple carcinogens are regularly detected in medications and continue to persist in the drug supply chain.

These contaminants are neither permanently eliminated nor effectively banned by regulatory authorities. Instead, the global scientific and regulatory communities appear to accept and tolerate the presence of carcinogens in over 95% of pharmaceuticals, raising urgent ethical and public health concerns.

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