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Ramipril Induced BCC and Dysplastic Nevus: Nitrosamine Contamination as Most Potential Trigger for The Development of Melanoma and Nonmelanoma Skin Cancer?

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A 76-year-old male presented himself to the dermatology department with primary complaints of a lesion located on the nose dating for 4 months. In the last two months the patient noticed the lesion growing in size. In 2017 a "spot" appeared on the left cheek.

The patient reported four operations in the left nasal area resulting in recurrences over time. The surgical interventions were performed in 2016, 2017, 2022.

An appendectomy, cholecystectomy, femur fracture with subsequent implant replacement and pulmonary thromboembolism were also reported in the recent years.

From 2008 an arterial hypertension was diagnosed for which the patient was taking the following medications: metoprolol succinate 50 mg once in the morning; from 2010 – ramipril 5 mg once at night and from 2022 apixaban 5 mg once in the morning and once in the evening.

No reports for malignancy in any family member, no allergies nor painful sunburns in the nose area declared. The patient requested a further therapeutic approach to be established.

The dermatology examination showed in the left ala of the nose, a papule with a pearly edge, superficial telangiectasias and a waxy appearance [Figure 1a]. The lesion was suspected for basal cell carcinoma. Above the left nasolabial fold a plaque with uneven pigmentation was observed – suspected for lentigo maligna [Figure 1b]. In the left axillary region, a tumor-like formation with an irregular shape and inhomogeneously distributed brown to black pigmentation was noticed– suspected for a dysplastic nevus [Figure 1c and 1d].

A change of therapy was recommended from the cardiologist: Ramipril administration was stopped and lercanidipine hydrochloride 10 mg was given once in the morning, metoprolol succinate 50 mg once in the morning, apixaban 5 mg twice daily – once in the morning and once in the evening.

Apixaban was stopped 48 hours before surgery and replaced for the time period with enoxaparin natrium 0,6 ml subcutaneously. In the morning before the surgical intervention the enoxaparin natrium was cancelled. After surgery the patient was switched again on apixaban 5 mg twice daily – once in the morning and once in the evening.

The surgical interventions of the suspected lesions were done under local anesthesia with lidocaine 2%. The lesions suspected for bcc and lentigo maligna were preoperatively marked [Figure 2a]. The tumorous formation located on the left dorsal nasal area was removed with an elliptical excision[Figure 2b]. The histology showed skin and subcutaneous tissue with smoothed dermoepidermal relief with hyperparakeratosis in the dermis and hemorrhages; small nests on the periphery of basal cell carcinoma, staged T1N0M0. The histological picture of the lesion located over the left nasolabial fold corresponded (after surgical removal) to lentigo benigna [Figure 2b]. The excision of the dysplastic nevus in the left axillary region resulted in histology as dermal pigmented dysplastic low grade nevus with a solar elastosis.

The remaining defects were closed by adjusting the edges with single interrupted sutures [Figure 2c and 2d].

Skin cancer can be considered as the most common neoplasm globally [1]. The annual incidence risk is increasing and we, as clinicians, should be questioning its multifactorial genesis [1]. Risk factors are perceived as an important prognostic element in every diagnosis [1]. Definitive diagnosis with a skin biopsy followed by a thorough histopathological examination remains as a gold standard in the diagnostic process [2]. Skin cancer can be divided into two categories – melanoma (MSC) and non-

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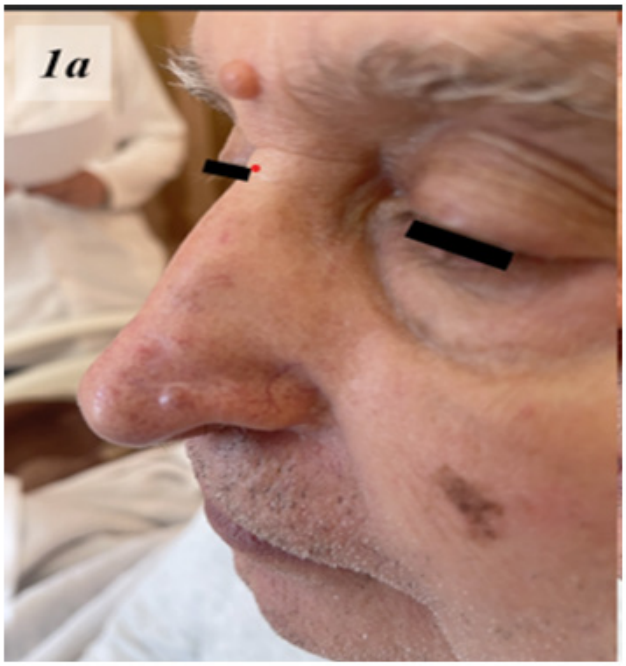
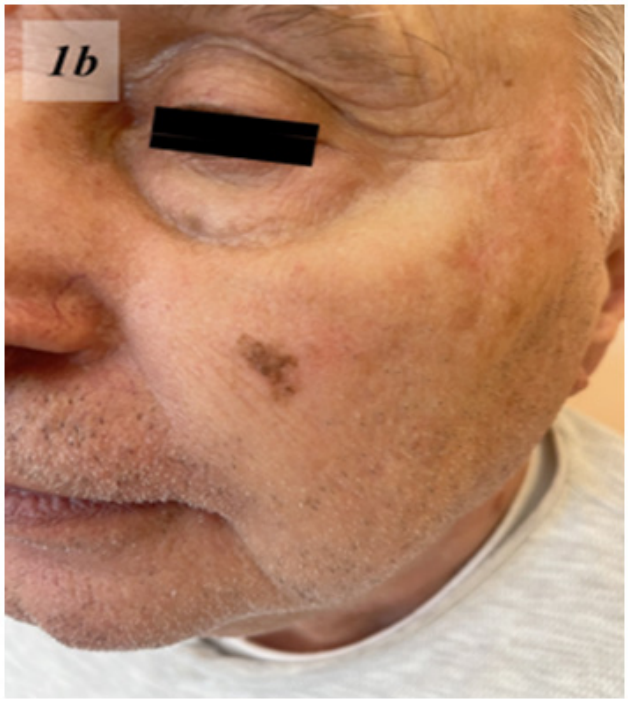


Figures 1a: A papule with a pearly edge, superficial telangiectasias and a waxy appearance located in the left ala of the nose.



Figures 1b: A plaque with uneven pigmentation located above the left nasolabial fold.

melanoma skin cancer (NMSC)[2]. Basal and squamous cell carcinoma are the most common types of NMSC [2]. In terms of percentage, the melanoma type of skin cancer accounts for nearly 2% of all skin malignancies but opposes a serious public health problem as it results in more death in the population [2]. In contrast, basal cell carcinoma is the most common type of NMSC and is perceived as a slow but yet locally invasive type of skin tumour[2].

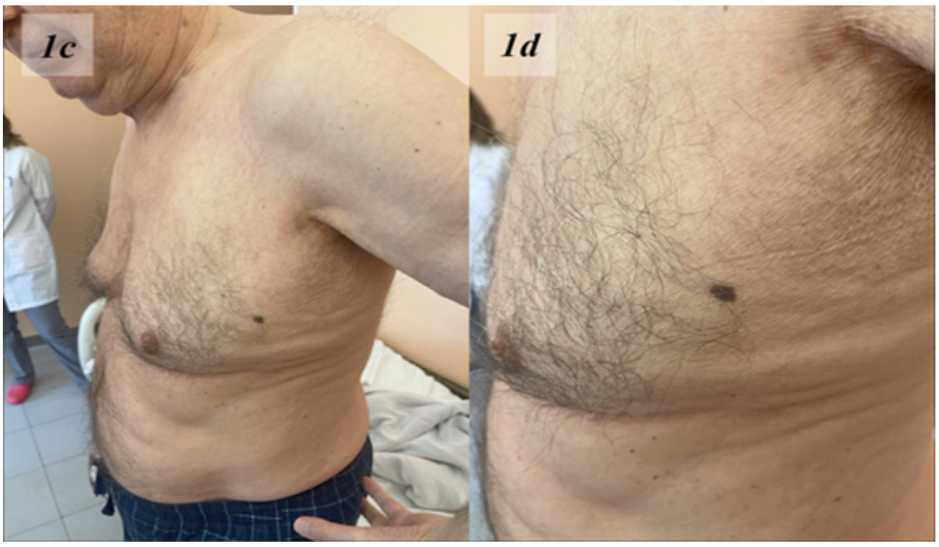


Figure1c, 1d: Tumor-like formation with an irregular shape and inhomogenously distributed black-brown pigmentation was noticed located in the left axillary region.

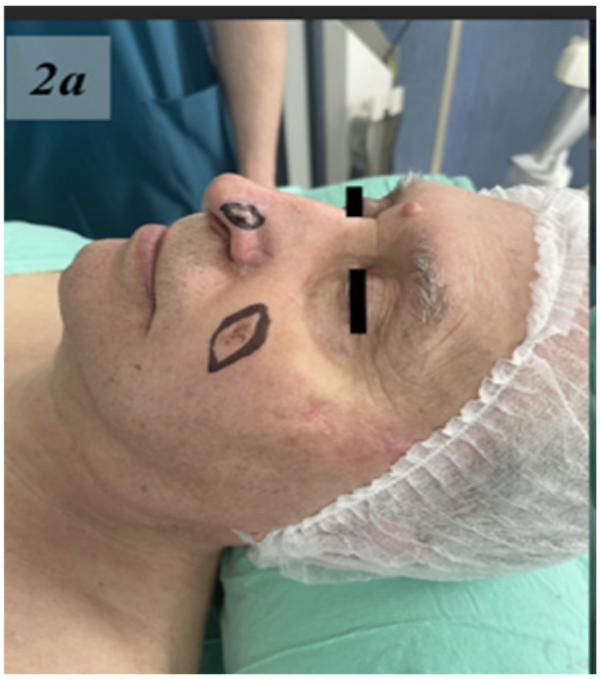


Figure2a: The lesions suspected for bcc and lentigo maligna were preoperatively marked.

N-nitrosamines are well-studied mutagens that have the ability to generate different types of cancers [3]. A cohort study performed by Hidajat et al has linked N-nitrosamines and the risk of cancer mortality [3]. The estimated cancer risk was nearly 94% for cancers of the lung, stomach, bladder, esophagus, and pancreas, liver, prostate, leukemia and multiple myeloma [3].

Expert group opinions seem to have acknowledged the significance of the issue with the nitrosamine-contamination making the problem "rather a reality than a myth"[4, 5].

Different types of medications have been linked with the potential "availability" of these mutagens, resulting in various forms of skin cancer: melanoma or/ and non-melanoma skin cancer [5-7].

Figure2b: Elliptical excision ofthe tumorous formation located on the left dorsal nasal area. Surgical excision of the plaque with uneven pigmentation above the left nasolabial fold.

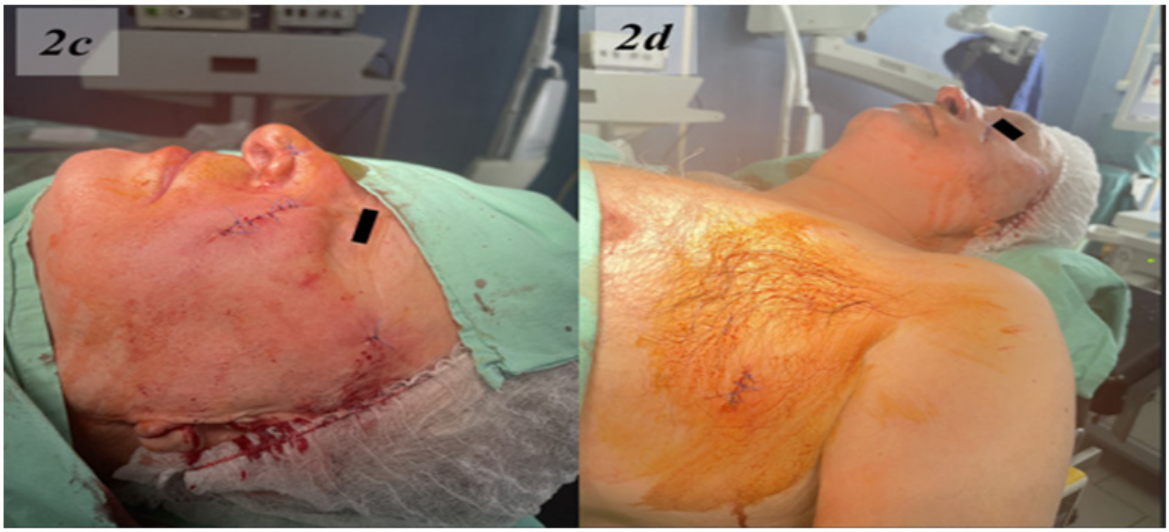


Figure2c, 2d: The remaining defects in the nasal and nasolabial fold areas (c) and the lesion in the left axillary region (d) were closed by adjusting the edges with single interrupted sutures.

Cutaneous melanoma is considered as one of the most dangerous cancers since the cancerous cells can quickly metastasize in different organs of the human body [8]. The aggressive behavior resulting in distant metastases and secondary lesion formations has earned its bad reputation among the other cancers [8].

Cardiovascular diseases are more common than cancer being one of the main causes for death in the human population [9]. With over 1 billion case reports globally, arterial hypertension is classified as the most frequent chronic disorders in the population resulting in various complications if left untreated [10]. Antihypertensive medications, such as beta-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin 2 receptor blockers and diuretics, are prescribed for

a primary treatment of hypertension [10].

Ramipril is a second generation angiotensin converting enzyme inhibitor (ACEi) that is used for the treatment of mild to moderate essential hypertension [11]. According to the analysis performed by Becker et al lisinopril (an ACE inhibitor) and losartan (an ARB) stimulates MV3 melanoma cell migration and invasion [8]. Promotion of tumor metastasis should not be overlooked and requires more attention to be brought on the subject [8].

Modern antihypertensive therapy with ACE inhibitors and ARBs is used on a daily basis in the treatment for arterial hypertension [8]. However, their administration remains controversial [4]. Almost certainly their "problematic" behavior can be explained with the potential carcinogenic impurities – the nitrosamines [4]. It is considered that the direct contact to nitrosamines exposure to rubber dust via inhalation for example can induce the transformation of a normal cell to a cancerous one and the manifestation of different cancer types in humans [3].

Nitrosamine-contamination is linked with the development of both melanoma and non-melanoma skin cancer in different independent case reports [6, 7, 12-14].

An important retrospective analysis provided by Nardone et al. associated the melanoma and non-melanoma skin cancer development with the administration of ACE inhibitors, ARBs and thiazides [15][Figure 3].

3 Skin Cancer Associated with Exposure to Antihypertensive Drugs

Table 3 Unadjusted and adjusted ORs[a] with 95% CIs of skin cancer for antihypertensive exposed and unexposed controls

	Reference	Basal cell carcinoma	Squamous cell carcinoma	Malignant melanoma
ACEIs				
Exposed, *n* (%)	27,134 (25)	533 (1.96)	182 (0.67)	187 (0.67)
Unexposed, *n* (%)	81,399 (75)	772 (0.95)	217 (0.27)	232 (0.29)
Unadjusted OR (95% CI)	1	2.09 (1.87–2.34)	2.53 (2.07–3.08)	2.42 (2.00–2.95)
Adjusted OR (95% CI)	1	2.23 (1.78–2.81)	1.94 (1.37–2.76)	1.71 (0.97–3.00)
ARBs				
Exposed, *n* (%)	13,818 (25)	283 (2.05)	106 (0.77)	96 (0.69)
Unexposed, *n* (%)	41,454 (75)	397 (0.96)	128 (0.31)	127 (0.31)
Unadjusted OR (95% CI)	1	2.16 (1.85–2.52)	2.50 (1.93–3.23)	2.25 (1.73–2.94)
Adjusted OR (95% CI)	1	2.86 (2.13–3.83)	2.22 (1.37–3.61)	1.24 (0.54–2.85)
Thiazides				
Exposed, *n* (%)	15,166 (25)	262 (1.73)	130 (0.86)	99 (0.65)
Unexposed, *n* (%)	45,498 (75)	457 (1.00)	132 (0.29)	145 (0.32)
Unadjusted OR (95% CI)	1	1.73 (1.49–2.02)	2.97 (2.33–3.79)	2.06 (1.59–2.66)
Adjusted OR (95% CI)	1	2.11 (1.60–2.79)	4.11 (2.66–6.35)	1.82 (1.01–3.82)

ACEIs angiotensin-converting-enzyme inhibitors, *ARBs* angiotensin-receptor blockers, *CCI* Charlson Comorbidities Index, *CI* confidence interval, *OR* odds ratio

[a] The ORs have been adjusted for age, gender, race and the CCI

Figure 3: Table from Nardone B et al.: Skin cancer associated with exposure to antihypertensive drugs [15].

The OR odds ratio for malignant melanoma after ACE inhibitors is estimated at: unadjusted OR (95% CI) 2.42 (2.00-2.95) and adjusted OR: (95%CI) 1.71(0.97-3.00); after ARBs unadjusted OR (95% CI) 2,25 (1,73-2,94) and adjusted OR (95% CI) 1.24 (0.54-2.85); and after thiazide use: unadjusted OR (95% CI) 2.06(1.59-2.66) and adjusted 1.82(1.01-3.82)[15].

From the table 3 it can be concluded, that the risk for developing melanoma is slightly higher with the thiazide use (adjusted 1.82) compared to the ACEi (1.71) and ARBs(1.24) after adjusting the ratio for age, gender, race and the CCI [15].Still the ACE inhibitors are with greater risk for melanoma development in comparison to the sartans (ARBs) [15].

According to the same study the estimated cancer risk for basal cell carcinoma development after: ACEi therapy is unadjusted OR (95% CI) 2.09 (1.87-2.34) and adjusted OR (95% CI) 2.23 (1.78-2.81); after ARBs unadjusted OR (95% CI) 2.16 (1.85-2.52) and adjusted OR (95% CI) 2.86 (2.13-3.83); and after thiazide use unadjusted OR (95% CI) 1.73 (1.49-2.02) and adjusted OR (95% CI) 2.11 (1.60-2.79)[15].

It can be concluded that the estimated cancer risk for BCC development after therapy with ARBs is slightly higher (2.86) than the therapy with ACEi (2.23) and thiazides (2.11) after adjusting the odd ratio [15].

The estimated simultaneously risk for the development of melanoma, BCC and squamous cell carcinoma (and probably also for dysplastic nevi) after therapy with ACEi, Sartans (ARBs) and

thiazides (15) (fig 3) suggests that the active substance of these drugs is possibly not responsible for the skin cancer development, as the mechanism of action of the medications is a completely different one.

For a long period of time the question remained open: What common "ingredient" found in the different medications classes might be responsible for the skin cancer development and progression? The question was indirectly answered in March 2022 by the pharmaceutical company Pfizer which announced the withdrawal of the medication quinapril HCL/hydrochlorothiazide due to the N-Nitroso-Quinapril contamination [16].

In practice, this gesture by Pfizer brings ACE inhibitors and thiazide diuretics into the category of potentially nitrosamine-contaminated blood medications (as a whole, affecting probably different pharmaceutical companies) and provides a more than eloquent explanation for the results of Nardone B et al. from 2017 [15] [Figure 3].

Another important issue is the introducing a daily acceptable dose for a known mutagen/carcinogen which practically seems to be a significant problem.

In practice, patients are exposed to a long-term risk arising from direct, daily contact with mutagens, carcinogens. Allowed by regulatory authorities, but not indicated on the leaflets of the affected batches of medicines.

In conclusion, we present a patient with arterial hypertension who had been taking ramipril for 13 years, developed basal cell carcinoma in the area of the nose with four recurrences after surgical excisions, a lentigo benigna in the left nasolabial fold area and a dysplastic nevus in the left axillary region. A histological verification was performed and the lesions were excised.

The role of nitrosamines as potential/real contaminants in ACE inhibitors and the possible melanoma or/and keratinocyte cancers development after systemic therapy is discussed. Rapid and adequate inspections of the possible nitrosamine contamination by the regulatory authorities at a national or/and international level will be needed in terms of solving the mystery called "carcinogenesis".

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