Symbiosis

ISSN Online: 2378-1726
www.symbiosisonlinepublishing.com

Letter to Editor | Clinical Research in Dermatology: Open Access | Open Access

SCC of the Nose and Metatypical BCC of the Shoulder Developing during Treatment with Valsartan/ Chlortalidone: Nitrosamine Contamination as Main Skin Cancer Triggering Factor

Kordeva S[1], Marchev S[2], Batashki I[3], *Tchernev G[1,4]

[1]*Onkoderma- Clinic for Dermatology, Venereology and Dermatologic Surgery, General Skobelev 26, 1606 Sofia, Bulgaria*

[2]*Head of Clinic of Cardiology, Medical Institute of the Ministry of Interior, 79 Skobelev Blv, 1606 Sofia, Bulgaria*

[3]*Chief, Director of the Medical Institute of Ministry of Interior, General Skobelev 79, 1606, Sofia, Bulgaria*

[4]*Department of Dermatology and Venereology, Medical Institute of Ministry of Interior, General Skobelev 79, 1606, Sofia, Bulgaria*

Received: March 27, 2023; Accepted: March 30, 2023; Published: April 06, 2023

***Corresponding author:** Georgi Tchernev, Department of Dermatology, Venereology and Dermatologic Surgery, Medical Institute of Ministry of Interior, MI-MVR, General Skobelev 79, Sofia, Bulgaria, E-mail: georgi_tchernev@yahoo.de*

A 75-year-old male presented himself in the department with primary complaints of a slowly progressive formation in the area of the nose dating from about 6 months. A punch biopsy was taken before hospitalization which resulted in keratinizing squamous cell carcinoma G2 with deep infiltration to the level of the sweat glands, staged later as T1N0M0.

No reported allergies or any malignancy in any family member. In 2020 the patient reported a surgical excision of a lesion located in the right shoulder area which resulted in the confirmation of the diagnosis metatypical BCC with clear resection lines.

Comorbidities: gonarthrosis, combined otoneurological syndrome, bilateral sensorineural hearing loss. In 2013 the patient was diagnosed with arterial hypertension for which he was taking Valsartan 160 mg once daily for nine years (until 2022) and then the therapy was switched to Chlortalidone 12.5 mg once daily.

The patient requested a physical examination and further therapeutic approach to be established.

The dermatological examination showed a cicatrix over a red scaly tumor formation located on the apex of the nose - a condition after the punch biopsy. Around the cicatrix a slight discoloration can be observed. In the right shoulder area a cicatrix from the past surgical intervention can be seen (Figure 1a) Lymph nodes were not palpable. The patient denies painful sunburns in the past.

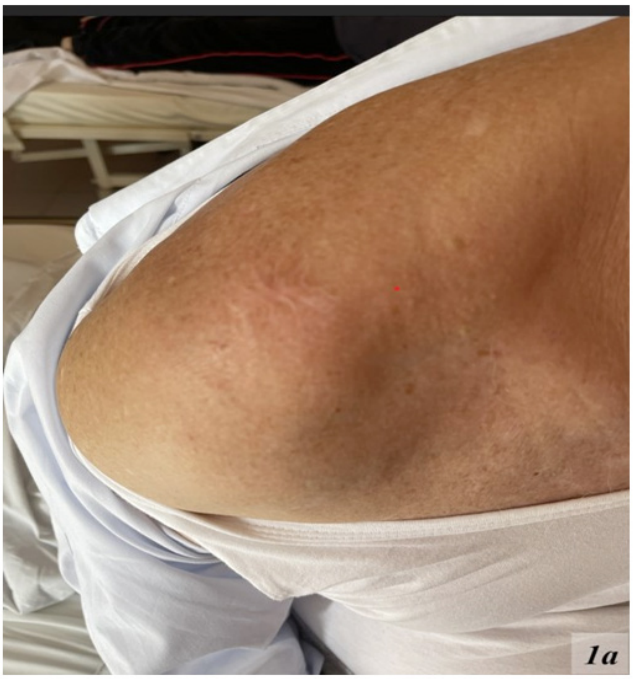
Routine blood tests were done without significant abnormalities. The patient was recommended a surgical excision under a local anesthesia.

In the area of the cicatrix, the formation was removed via an elliptical excision under local anesthesia.The operative wound was closed by adjusting the edges and suturing with single interrupted sutures (Figure1b) The histology was negative for tumor cells; slight inflammation with clean resection lines was noted. Daily dressings with povidone-iodine for 7 days were performed. A recommendation was made from cardiologist for anambulatory change in the patient's antihypertensive therapy with different medications than ACE inhibitors, angiotensin receptor blockers and thiazides.

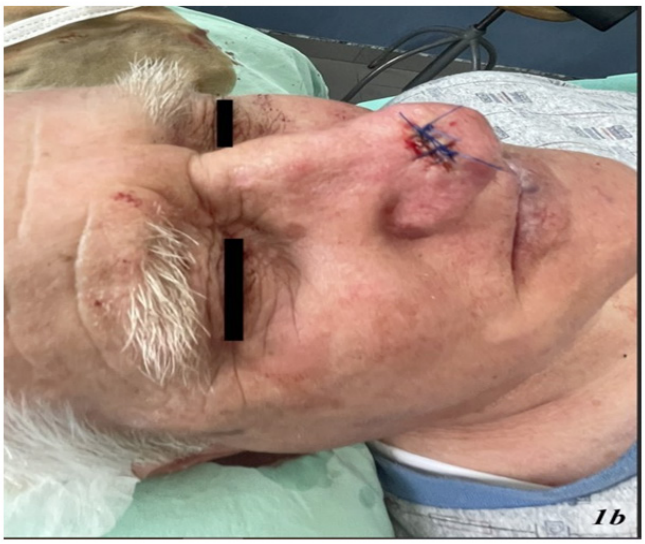
Cutaneous squamous cell carcinoma (cSCC) is rated as the second most common non-melanoma skin cancer [1]. A diagnostic criteria for cSCC verification remains the skin biopsy [1]. A well-performed biopsy can show us the depth of invasion, the level of differentiation and lymphovascular infiltration [1]. In our case report, the punch biopsy was not only used for a diagnostic but also a therapeutic approach. The reexcision of the lesion was negative for tumor cells, only a slight inflammation was observed.

Although the UV exposure, fair skin (Fitzpatrick types 1-3) and immunosuppression can increase the risk for developing cSCC, independent expert opinions, studies and analysis are proving that contamination with nitrosamines can also be considered as a triggering factor for cancer development [1-3]. A strong connection between nitrosamines and the development of different types of cancer was established in a significant cohort study by Hidajat et al [2]. In terms of cancer development, the experts find a direct correlation between the inhalation of nitrosamine containing dust and an increased cancer mortality risk [2]. Their "availability" was found in different classes of medications –antidiabetic medications/metformin, ranitidine, antihypertensive drugs: ACE inhibitors, angiotensin receptor blockers/sartansand thiazide diuretics, causing different forms of skin cancer [4-6].

A meta-analysis of randomized controlled trials done by Sipahi et al, stated that the risk for new cancer development after



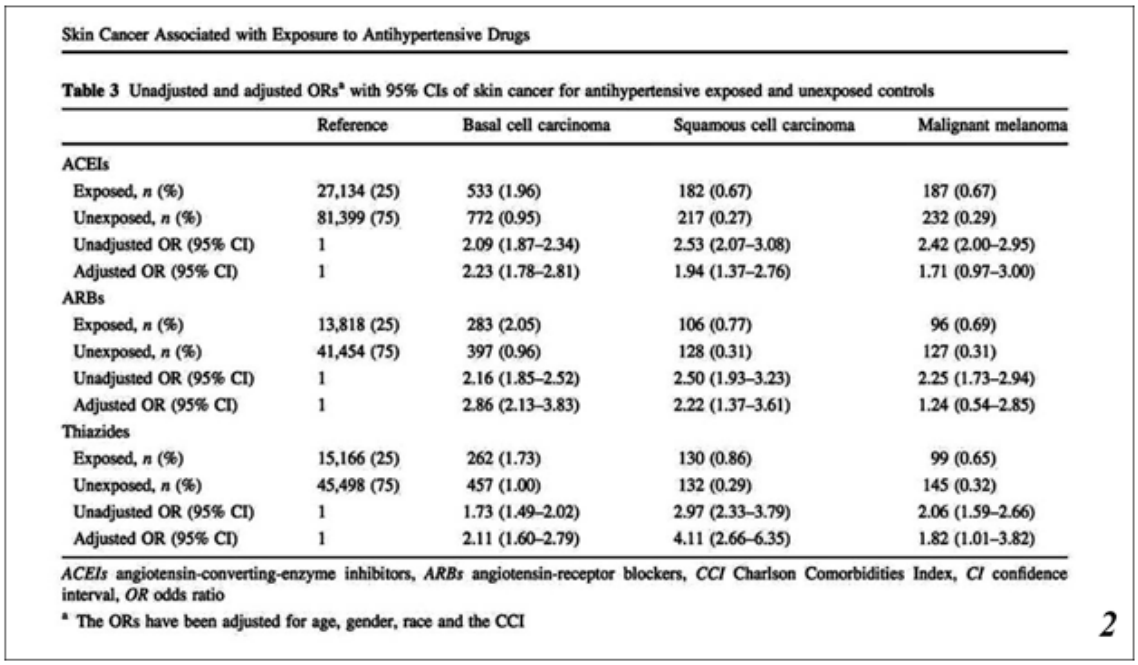
Figures 1a: A cicatricle lesion observed in the right shoulder area after surgical removal of metatypical BCC.



Figures 1b: Postoperative clinical image of the apex of the nose after removal of a small SCC

angiotensin-receptor blockers increases with the degree of cumulative exposure to these medications [7]. Since nitrosamines are potent carcinogens, the excess risk after long-term use of certain nitrosamine-contaminated medications has indeed public health implications [8]. The case study done by Li et al indicated that the estimated cancer risk for NDMA ranged from 40 to 126 additional cancer cases per 100,000 individuals exposed to the contamination, and 12 to 48 additional cancer cases per 100, 000 for NDEA exposure [8]. Another data presented by Olschewski et al. concluded that major consideration should be given when administrating AT1 antagonist (sartans) in hypertensive cancer patients, because this could be a trigger the progression of melanoma for example [9].

Nitrosamine contamination in commonly used antihypertensive drugs were linked with both melanoma and non-melanoma skin cancer [10-14]. Sartans and thiazide diuretics (hydrochlorothiazide) are well-documented in the scientific



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

2

Figures 2: Nardone B et al.: Skin cancer associated with exposure to antihypertensive drugs [16].

literature with the development of keratinocytic types of tumors – basal and squamous cell carcinomas [5,6,14,15].

An analysis made by Nardone B et al concluded that the estimated risk for keratinocyte tumors after monotherapy with sartans for SCCs was: unadjusted OR (95% CI): 2,50 (1,93-3,23), adjusted OR (95% CI): 2,22 (1,37-3,61)and for thiazide diuretic monotherapy for SCCs was: unadjusted OR (95% CI): 2,97 (2,33-3,79), adjusted OR (95% CI): 4,11 (2,66-6,35) [16] [Figure 2].

Another scientific paper by Schmidt SA et al observed an increased risk of SCC after diuretic use (OR 1.19; 1.06-1.33), followed by potassium-sparing agents alone (OR 1.40; 1.09-1.80) or with low-ceiling diuretics (OR 2.68; 2.24-3.21) and by long-term use (OR 1.41; 1.16-1.72 at low intensity; and OR 1.44; 0.98-2.14 at high intensity) [17].

A report from Sable et al associated an increased risk for SCC after use of ARBs: adjusted (OR:1.75 ; 95%CI:1.08-2.08), ACE: adjusted (OR:1.59: 95% CI: 1.12-2.25), TZ: adjusted (OR:3.47; 95%CI: 1.99-6.04) [18].

The pharmaceutical company Pfizer released in March 2022 a statement in which they announced a significant recall of the medication quinapril HCL/hydrochlorothiazide due to the N-Nitroso-Quinapril contamination [19]. This statement supports our thesis that carcinogenesis may be due to the availability of one common agent – the nitrosamines [3].

Chlorthalidone is a thiazide-like diuretic used in the treatment for hypertension by decreasing the intravascular volume though promoted diuretics are scarce [20]. Although the data in the literature are for a potential nitrosamine-contaminated thiazide diuretics, the thiazide-like diuretics (for example Chlorthalidone) might be also potentially contaminated with the mutagen?

In terms of skin cancer development and progression, the alterations within the p53 gene are the main cause for nearly 50% of all neoplasms [21]. Mutations in this particular gene and UV exposure are the factors that can result in skin cancer [21]. However, our patient had a negative family history for malignancy and denies painful sunburns in child- and adulthood.

In relation to the above mentioned analysis and expert opinions, we must ask ourselves as clinicians: Could the potential nitrosamine-contamination in the antihypertensive medications be a real reason for rethinking skin cancer's pathogenesis? A question we think is worth answering.

We present a patient on systemic therapy with Valsartan and Chlortalidone developing within the treatment regimen metatypical BCC of the shoulder and later keratinizing squamous cell carcinoma G2, staged T1N0M0.

Although the diuretic was administrated in the past one year, the therapy with Valsartan was taken for nine years. The potential nitrosamine-contamination in the angiotensin receptor blockers (sartans) and thiazide diuretics/ thiazide –like diuretics(?) in terms of skin cancer development is, once again, discussed.

References

1. Waldman A, Schmults C. Cutaneous Squamous Cell Carcinoma. HematolOncolClin North Am. 2019 ;33(1):1-12. doi: 10.1016/j.hoc.2018.08.001.
2. Hidajat M, McElvenny DM, Ritchie P, Darnton A, Mueller W, van Tongeren M, et al. Lifetime exposure to rubber dusts, fumes and N-nitrosamines and cancer mortality in a cohort of British rubber workers with 49 years follow-up. Occup Environ Med. 2019 ;76(4):250-258.doi: 10.1136/oemed-2018-105181.
3. Tchernev G, Kordeva S, Patterson JW. Nitrosamines and skin cancer: rather reality than a myth? J Med Review (Bulgarian). 2023;59: 5-7.
4. Tchernev G, Kordeva S, Marinov V, Batashki I, Batashki A, Patterson JW. Nitrosamines in antihypertensives, metformin and raniti-dine as cofactors for melanoma and development of other cancers. Expert group opinion. Port J Dermatol and Venereol. 2022;80(4): 332–334. DOI: 10.24875/PJDV.22000014.
5. 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. Georgian Med News. Epub ahead of print 2023. 335(1): 22-25.
6. Malev V, Tchernev G. Dysplastic nevus and BCC development after antihypertensive therapy with Valsartan and Hydrochlorothiazide!? ClinResDermatol Open Access 2019;6(5): 1–2. Doi: 10.15226/2378-1726/6/5/001105.
7. Sipahi I. Risk of cancer with angiotensin-receptor blockers increases with increasing cumulative exposure: meta-regression analysis of randomized trials. PLoS One. 2022; 17(3): e0263461. doi: 10.1371/journal.pone.0263461.
8. Li K, Ricker K, Tsai FC, Hsieh CJ, Osborne G, Sun M, et al. Estimated cancer risks associated with nitrosamine contamination in commonly used medications. Int J Environ Res Public Health. 2021;18(18): 9465. doi: 10.3390/ijerph18189465.
9. Olschewski DN, Hofschröer V, Nielsen N, Seidler DG, Schwab A, Stock C. The Angiotensin II Type 1 Receptor Antagonist Losartan Affects NHE1-Dependent Melanoma Cell Behavior. Cell PhysiolBiochem. 2018;45(6): 2560-2576. doi: 10.1159/000488274.
10. Tchernev G, Poterov G, Patterson JW, Malev V. Multiple verrucous carcinomas and giant acral melanoma developing after antihypertensive therapy with valsartan and olmesartan. J Medical Review (Bulgarian). 2020;56(5): 58-60.
11. Tchernev G, Bitolska A, Patterson JW. Telmisartan (and/or nitrosamine) - induced occult melanoma: first reported case in world literature. Expert Rev ClinPharmacol. 2021;14(9): 1075-1080. Doi: 10.1080/17512433.2021.1938547.
12. Tchernev G, Oliveira N, Kandathil LG, Patterson JW. Valsartan (or/and Nitrosamine) induced BCC and dysplastic nevi: current insights. Clin Res Dermatol Open Access 2021;8(4): 1–6. doi: 10.15226/2378-1726/8/5/001147.
13. Tchernev G, Kordeva S. Giant BCC of the scalp after telmisartan/amlodipine: potential role of nitrosamine contamination as main cause for skin cancer development. Port J Dermatol and Venereol. 2023. DOI: 10.24875/PJDV.23000001.
14. Tchernev G, Kordeva S, Batashki I, Batashki A, Cardoso JC, Oliveira N et al. SCC development after Irbesartan/Hydrochlorothiazide: potential role of nitrosamines as skin cancer triggering factors. Med Pregled (Bulgarian). 2023;59(3). 12-14.
15. Tchernev G, Lozev I, Pidakev I, Kordeva S. Karapandzic Flap For Squamous Cell Carcinoma of The Lower Lipp: Potential Role of Nitrosamines in Eprosartan as Cancer Triggering Factors. Georgian Med News. 2023; (334): 83-85.
16. Nardone B, Majewski S, Kim AS, Kiguradze T, Martinez-Escala EM, Friedland R, 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(3): 249-255. doi: 10.1007/s40264-016-0487-9.
17. Schmidt SA, Schmidt M, Mehnert F, Lemeshow S, Sørensen HT. Use of antihypertensive drugs and risk of skin cancer. J EurAcadDermatolVenereol. 2015 ;29(8):1545-1554. doi: 10.1111/jdv.12921.
18. Sable L, Majewski S, Nardone B, et al. Association of melanomaand non-melanoma skin cancer with antihypertensive drugs: A reportfrom the Research on Adverse Drug Events and Reports Project. JAm AcadDermatol. 2016; 74(5): AB221.Doi: 10.1016/j.jaad.2016.02.869.
19. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-voluntary-nationwide-recall-lots-accuretictm
20. Kerndt CC, Patel JB. Chlorthalidone. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. 2023.
21. Benjamin CL, Ananthaswamy HN. p53 and the pathogenesis of skin cancer. ToxicolApplPharmacol. 2007 ;224(3):241-248. doi: 10.1016/j.taap.2006.12.006.