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High Risk BCC of the Nose After Telmisartan Hydrochlorothiazide: Potential Role of Nitrosamine Contamination as Key Triggering Factor for Skin Cancer Development

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A 62-year-old male presented in the dermatology department with primary complaints of a 1-year-old lesion located in the right upper nose segment. He noticed the formation growing in size and changing its texture.

The patient denies having allergies or any malignancy in any family member. He has arterial hypertension for which he takes bisoprolol 10 mg once in the morning, amlodipine 10 mg once in the evening, spironolactone 25 mg once in the morning, atorvastatin 20 mg once in the evening and from 5 years till present telmisartan/hydrochlorothiazide 80/12.5 mg once in the morning.For five years the patient took clonidine hydrochloride 0.15 mg once daily and for a year - prazosin 2mg once daily. Now the clonidine hydrochloride is administered when needed.

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

The dermatological examination showed an elevated large lesion with crusts and regular borders located in the right upper nasal region, in close proximity to the right eye [Figure 1]. The lesion was suspected clinically for basal cell carcinoma.

Lentigo solaris and visible telangiectasias can be seen on the patient's face. Small in size lesion, located under the right eye, which was also suspected for bcc,was noticeablebut due to the patient's request it wasn't sent for histopathological verification.

A biopsy was taken, from the formation located on the nose, which resulted in abundant parakeratosis, atrophy of the epidermis with smoothing of dermo-epidermal undulations and a focus of superficial necrosis; proliferation of atypical basaloid keratinocytes, forming nests and pseudorosettes of various calibers with a palisade periphery, demarcated by fibrosis and a well-vascularized stroma. The histopathological picture corresponded to an infiltrative type of basal cell carcinoma.

Surgical removal of the lesion was recommended which the patient later on denied.

The link between nitrosamine exposure and human cancer development has been established in the world literature making the statement rather a reality than a myth [1,2]. "Exposure-response relationship" was found between NDMA and different types of human cancer – bladder, multiple myeloma, stomach, prostate, oesophagus and liver;with an increased risk for lung cancer, non-Hodgkin's lymphoma, brain and pancreatic cancers [1]. An elevated cancer mortality risk was established between the known carcinogen (the N-nitrosamines) and the carcinogenesis in humans [1].

According to Olchewski et al., angiotensin receptor blockers can interfere with the melanogenesis by decreasing the human melanoma (MV3) cells but at the same time increasing the adhesion and invasion of the melanocytes [3].

Angiotensin receptors are present in the melanocytic and keratinocytic tumors [4]. Regardless of this fact, the general opinion is that the pure (generic) substance/drug should not be responsible for the procarcinogenic effect of the medication.

Sartans and thiazide diuretics have been linked in the literature not only with the development of dysplastic nevi (which are associated with the de novo manifestation of melanoma) but also with basal cell carcinoma [4-6].

Potentially nitrosamine-contaminated antihypertensive medications have been linked with both melanocytic and non-melanocytic skin tumors by numerous case reports in the literature [4-10].

Telmisartan has been associated with the development not only for melanoma but for keratinocytic types of tumors, namely for basal cell carcinoma [5, 9]. The potential procarcinogenic

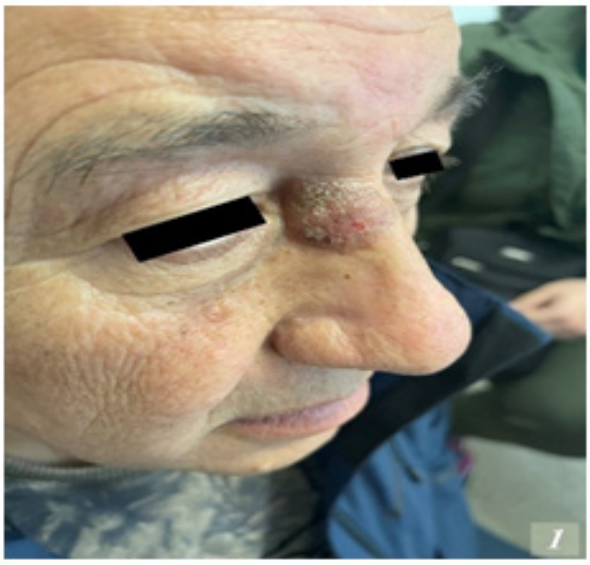

Figure 1: An elevated large lesion with crusts and regular borders located in the right upper nasal region, in close proximity to the right eye. Lentigo-solaris and visible teleangiectasias can be seen. Small in size lesion, located under the right eye.

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

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Figure 2: Nardone B et al.: Skin cancer associated with exposure to antihypertensive drugs [11].

effect, according to some experts, could be due to a possible contamination of nitrosamines in the antihypertensive therapy, which are well-known mutagens [5, 9].

According to Nardone B et al. the sartans are associated with a significant risk for basal, and squamous cell carcinomas [4-6, 9, 11, 12] [Figure 2/ Table 1). The estimated risk for developing keratinocyte tumors after monotherapy with sartans for BCCs: unadjusted OR (95% CI): 2,16 (1,85-2,52), adjusted OR (95% CI): 2,86 (2,13-3,83) and for SCCs: unadjusted OR (95% CI): 2,50 (1,93-3,23), adjusted OR (95% CI): 2,22 (1,37-3,61)[11]. A separated risk factor, for the development of both basal and squamous cell carcinomas according to the same article, is the thiazide diuretic monotherapy: for BCCs: unadajusted OR (95%

CI): 1,73 (1,49-2,02), adjusted OR (95% CI): 2,11; for SCCs: unadjusted OR (95% CI): 2,97 (2,33-3,79), adjustedOR (95% CI): 4,11 (2,66-6,35)[11]. A two-fold risk after monotherapy with thiazide diuretics for basal cell carcinoma and a four-fold risk for developing squamous cell carcinoma. So, if the separated risk after monotherapy is nearly two to four times higher for developing keratinocytic types of tumors, then the question remains open: What if the patient is on combined therapy – with potentially nitrosamine contaminated sartans and diuretics? Will the risk be higher? All these questions should be answered by the appropriate authorities in the face of FDA/ EMA in order to distinguish the exact correlation between the antihypertensive therapy and the carcinogenesis.

A systematic review and meta-analysis done by Shao, SC., Lai, CC., Chen, YH. et al. stated that Hydrochlorothiazide is indeed associated with an increased risk for melanoma and non-melanoma skin cancer in non-Asian countries [13].

In March 2022 the pharmaceutical company Pfizer announced that they are recalling lots of quinapril HCl/hydrochlorothiazide tablets due to the N-Nitroso-Quinapril contamination [14]. This statement can conclude that the thiazide diuretics may be a separate additional risk for the development of not only skin cancer but also for different types of neoplasm.

It is important for future investigations by the FDA/EMA of medications contaminated with nitrosamines to announce their type and exact concentration in order to clarify their pathogenetic significance.

Nitrosamine-induced carcinogenesis seems to be the new reality nowadays. Following the cohort studies and analysis, the different expert opinions and even the single case reports, we can conclude that the potential contamination with nitrosamines in the different drug classes of antihypertensive medications (sartans, ACE inhibitors, diuretics), ranitidine and metformin, is indeed a triggering factor for the development of different neo plasms and especially skin cancer [8, 1-13].

We present a patient on systemic therapy for arterial hypertension with bisoprolol, amlodipine, spironolactone and telmisartan/ hydrochlorothiazide. Given the anamnestic data – the absence of painful sunburns and the potential nitrosamine contamination in the above presented medications, we can conclude that the possible nitrosamine contamination is in all likelihood the reason for the development of the patient's basal cell carcinoma.

References

1. 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.
2. Tchernev G, Kordeva S, Patterson JW. Nitrosamines and skincancer: rather reality than a myth? J Med Review (Bulgarian).2023;59:5-7.
3. 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.
4. Tchernev G, Oliveira N, Kandathil LG, Patterson JW. Valsartan (or/ andNitrosamine) 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.
5. Tchernev G, Bitolska A, Patterson JW. Telmisartan (and/or nitrosamine) - induced occult melanoma: first reported case inworld literature. Expert Rev Clin Pharmacol. 2021; 14(9): 1075-1080. Doi 10.1080/17512433.2021.1938547.
6. Malev V, Tchernev G. Dysplastic nevus and BCC development afterantihypertensive therapy with Valsartan and Hydrochlorothiazide!? Clin Res Dermatol Open Access. 2019; 6(5): 1–2. Doi: 10.15226/2378-1726/6/5/001105.
7. Tchernev G, Poterov G, Patterson JW, Malev V. Multiple verrucouscarcinomas and giant acral melanoma developing after antihypertensivetherapy with valsartan and olmesartan. J Medical Review (Bulgarian). 2020;56(5): 58-60.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. Shao SC, Lai CC, Chen YH, Chia-Cheng Lai E, Hung MJ, Chi CC. Associations of thiazide use with skin cancers: a systematic review and meta-analysis. BMC Med. 2022;20(1): 228. doi: 10.1186/s12916-022-02419-9.
14. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-voluntary-nationwide-recall-lots-accuretictm