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 (Figure 1b). 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 an ambulatory 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 – anti-diabetic medications/metformin, ranitidine, antihypertensive drugs: ACE inhibitors, angiotensin receptor blockers/sartans and 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
SCC of the Nose and Metatypical BCC of the Shoulder Developing during Treatment with Valsartan/ Chlortalidone: Nitrosamine Contamination as Main Skin Cancer Triggering Factor

Figures 1a: A cicatricial 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.

Figures 1a: A cicatricial 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.

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 et al. concluded that major consideration should be given when administering AT1 antagonist (sartans) in hypertensive cancer patients, because this could be a trigger the progression of melanoma for example [9].

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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


