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Valsartan (or/and Nitrosamine) Induced BCC and Dysplastic Nevi: Current Insights

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Abstract

Introduction: Contamination of drugs for high blood pressure (sartans/ angiotensin receptor blockers) with nitrosamines occurs during the manufacturing process and has proven to be a serious international health problem. The reason for this problem is that the 4 nitrosamines discovered so far have been associated with the simultaneous or gradual development of cutaneous tumors as well as tumors of other organ systems. The presence of angiotensin receptors in melanocytic and keratinocytic tumors and their metastases adds difficulty when attempting to determine the relative importance of each of these two components (i.e. nitrosamines and angiotensin receptors) in the context of carcinogenesis.

Case report: We report a 40-year-old patient with arterial hypertension with a duration of skin complaints of about 7 months, clinically manifested by 1) the appearance of a solitary tumor near the medial corner of the left eye, verified histologically as Basal Cell Carcinoma (BCC), and 2) multiple, eruptive dysplastic nevi in the area of the posterior sweat gutter. The patient's systemic medications included: bisoprolol 5mg (1-0-1 / 2) and indapamide 1.5mg (1-0-0), taken for one year, and 2 years of treatment with amlodipine / valsartan - 5 mg / 160 mg (1-0-1/2) for an initial period of 1 year, followed by a reduced dose of (1/2-0-0) for an additional year.

Conclusion: We report the simultaneous development of basal cell carcinoma and dysplastic nevi after the use of a preparation containing generic valsartan. We discuss 1) the role of nitrosamines as possible major factors in the development of dysplastic nevi and BCC; 2) the possible effect of sartans themselves on angiotensin receptors in the skin and: 3) a new, innovative scheme for treatment of drug-induced BCC by cryoimmunotherapy.

Keywords

Nitrosamines; Valsartan; Angiotensin Receptor Blockers; Arterial Hypertension; Melanoma; BCC; Cryoimmunotherapy

Introduction

Drug-mediated carcinogenesis is a complex process in which the development of single or multiple neoplasms is observed after initiation of a particular drug therapy [1]. The process of induction of a certain neoplastic cell branch can be driven by different mechanisms and proceeds through the stages of (1) initiation, (2) tumor promotion and (3) progression of a premalignant to a malignant lesion (2). Nitrosamines have long been known as important initiating factors in carcinogenesis [2]. The transition to the third phase mentioned above could be spontaneous or potentiated by mutagens or other initiating agents [2]. Whether the active component of the drug itself, or impurities in the form of nitrosamines, are to blame for this process remains a mystery [1,3]. The lack of follow-up evidence to clarify the troubling data shared in 2015/2016 regarding the use of sartans/ angiotensin receptor blockers and the risk of developing various skin tumors is at least concerning [1,4,5]. However, this evidence is probably multifactorial [1,6,7]. The introduction, monitoring and recording of so called "dose-dependent time intervals for generating a neoplastic cell clone" or "for the transformation of an existing normal one into a pathological/ tumor one" are steps in the right direction [7]. The reason is that they show a certain stereotypical clinical behaviour and recurrence of events and processes that can then be further analysed [7]. The stereotypical recurrence is indicative of existing dependencies or potentially causal relationships [7].

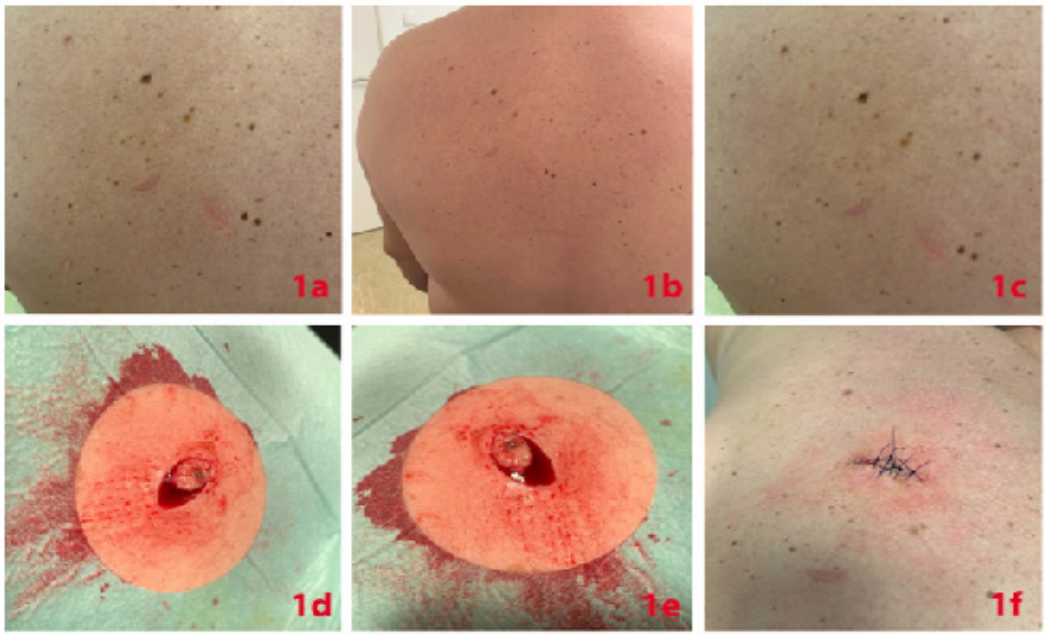
Another question is, what are the exact mechanisms leading to the end condition defined by us as a tumor [2]? Tumor development may be potentiated by: 1) the active ingredient of a particular drug (although unlikely) [8-10], in this case the sartan/ angiotensin receptor blocker (due to the established presence of angiotensin receptors in the skin [11]); and 2) contaminants in the form of nitrosamines (four so far, according to official data), causing up to 15 different tumors (very likely) [1,3]. Thus far, the dynamics of development of skin neoplasms (epithelial and melanocytic) show that they could be dose-dependent [1,7] and that they can occur regardless of whether the agents are generics or original sartans [1,7]. This "stereotypical tumor behaviour" has been established in our clinical observations [1,7]. A further issue revolves around another possible unifying pathogenetic factor: the presence or absence of nitrosamines, as well as their quantitative identification [1,7]. In practice, the presence or absence of nitrosamines has been difficult to establish (being often institutionally and geographically determined) [1,3,6-9,12]. Interestingly, this difficulty in itself has tended to promote additional focus on the potential role of nitrosamines as a key one in tumor development [1,3,12].

Case Report

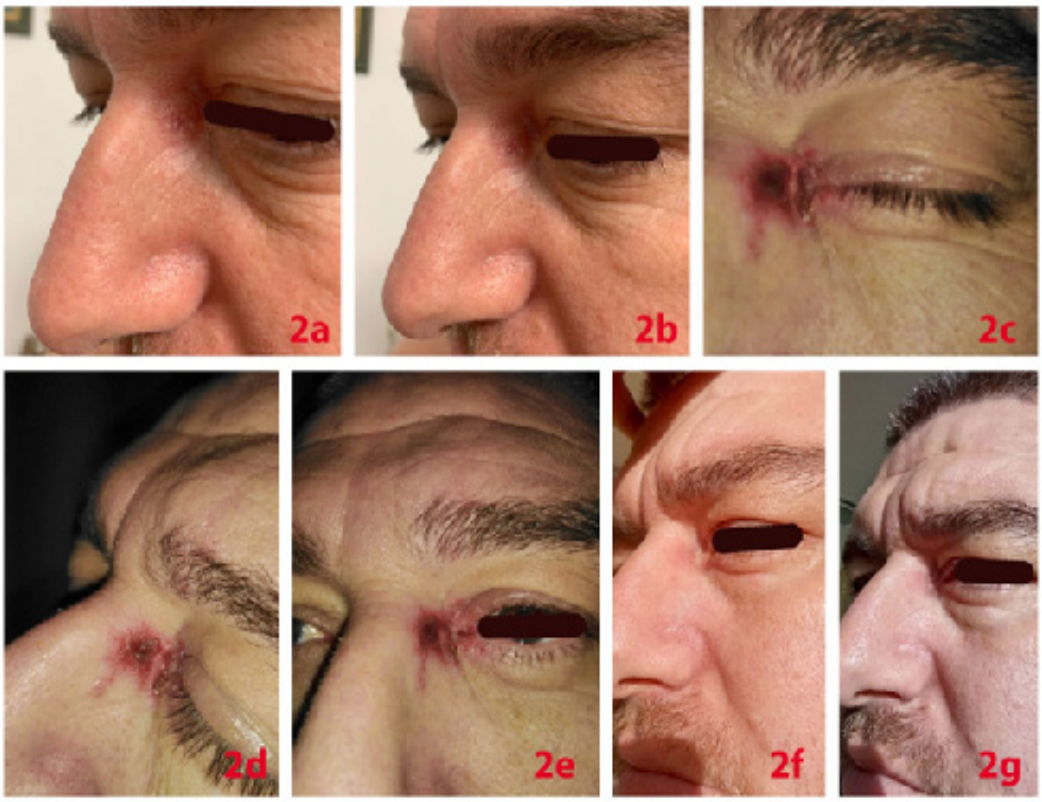
We report the case of a 40-year-old patient who presented in the dermatology clinic with medical complaints of about 6-7 months duration. He reported: 1) multiple pigmented lesions on the upper back, and 2) the parallel appearance of a solitary, slightly raised tumor-like lesion located in close proximity to the left medial canthus (figures 1a-c, 2a, 2b). An ambulatory biopsy of the latter showed a high-risk superficial basal cell carcinoma. There are no anamnestic data on painful sunburns in the past, and there is no information about the presence of skin cancer in relatives.

For about 2 years, the patient has carried a diagnosis of arterial hypertension. The patient's current medications include: bisoprolol 5mg (1-0-1 / 2) and indapamide 1.5mg (1-0-0), taken for one year, and 2 years of treatment with amlodipine / valsartan - 5 mg / 160 mg (1-0-1 / 2) for an initial period of 1 year, followed by a reduced dose of (1 / 2-0-0) for an additional year up to the time of the review.

At the time of his dermatological examination we found multiple acquired eruptive melanocytic nevi with minimal diameter on the upper back, some of which - clinically and dermatoscopically - met criteria for dysplastic nevi (figures 1a-1c). Surgical excision was performed on one melanocytic nevus (figures 1d, 1e, 1f), which subsequently revealed histological evidence of dysplastic nevus, with clear resection margins. Regarding the histologically-identified superficial basal cell carcinoma of the left canthal area, cryo-immunotherapy (cryo-spray) was planned and initiated due to the patient's refusal to undergo surgical treatment (figures 2a-2g): Lesions were treated using a CRY -AC container (Brymill Cryogenic Systems, Ellington, Connecticut) at a distance of 4 to 5 cm for a period of approximately 8 seconds for initially 4 cycles at day 1, obtaining a 2-mm margin around the histopathologically-estimated tumor lesion. Immediately after the spray session with liquid nitrogen (same day), the patient was instructed to apply a thin coat of imiquimod 5% cream for 5 consecutive nights, to take 2 days off, and repeat for a total of 6 weeks. During the first cryo-immuno-session, about the time of the 3rd application of imiquimod 5% cream, we observed the development of local inflammation, followed by abundant secretion in the form of transudate, perilesional redness, and severe pain in the medial corner of the eye, due to which treatment was temporarily discontinued immediately after the fifth day (figures 2c, 2d). Systemic antibiotic treatment with clarithromycin 500 mg, once daily for 10 days, was started in combination with silver sulfadiazine cream 1% twice daily (topical therapy) for 10 days (figures 2e, 2f). Subsequently, topical therapy was replaced by 3 times daily administration of a complex gel containing vitamin E, provitamin B5 and medical silicones, for an additional period of 5 days (figures 2f, 2g). We observed significant regression of the lesion, beginning in the periphery, followed by complete healing and a good cosmetic result (figure 2g). The patient was informed of the need to follow regular monthly clinical check-ups for a minimum of one year in order to rule out local recurrence.



Figures 1a-1c: Multiple acquired melanocytic nevi in the dorsal area, some of which are dysplastic
Figures 1d-1f: Surgical removal of a dysplastic nevus by elliptical excision under local anesthesia and closure of operative defect by of single skin sutures



Figures 2a, 2b: High-risk basal cell carcinoma adjacent to the medial corner of the eye on the left. The diagnosis was verified histopathologically by skin biopsy
Figures 2c, 2d, 2e: Clinical picture after treatment with one session of cryoimmunotherapy
Figures 2f, 2g: Clinical picture after 21 days, followed by complete clinical remission

Discussion

This seemingly trivial case is interesting from 3 main points of view: 1) Innovative treatment of high-risk non-melanocytic skin tumors with a new treatment regimen, 2) drug mediated carcinogenesis - in this case the drug valsartan, which could be considered as a possible pathogenetic trigger for generating melanocytic and non-melanocytic skin tumors and 3) the most important one about the possible role of nitrosamines as triggers of malignant skin tumors.

High-risk basal cell carcinomas are a challenge for dermatologists and often require specialized management using the known standard surgical approaches: elliptical excision, Mohs surgery, and plastic reconstructive surgical techniques, including the various types of rotational or transposition flaps for covering the defects [13-15]. Skin transplantation in the form of full-thickness mesh grafts or split skin mesh grafts also proves to be a good option, the application of which depends on the degree of involvement of underlying tissues, the patient's desire to achieve optimal cosmetic results, and the recommendations of the surgical team [16].

Cryoimmunotherapy is proving to be an effective method to treat basal cell carcinomas, especially superficial variants and those less than 2 cm in diameter or in hard-to-reach or especially risky areas in terms of a number of anatomical features [17,18]. The method is not widespread, but is of proven effectiveness in both superficial and non-superficial basal cell carcinomas and squamous cell carcinomas (in situ) with variable localization [17,18].

The reported schemes for the duration and intensity of cryosessions vary and, given the limitations of hard data, this makes the sharing of individual experiences especially significant and desirable.

Drug-mediated / induced carcinogenesis has been the subject of lively debate since 2015/2016/2017 [19-21]. It is within this time interval that research teams first alerted the medical public to the possible role of angiotensin receptor blockers / sartans as inducers or risk factors in the development of melanoma and basal cell carcinoma [19-21]. However, at the time of publication of the 2017 data, it was not known whether or not the respective batches of drugs contained nitrosamines [19-21]. International inspections for this purpose were begun only in 2018 [3]. This is what created the possibility for a kind of "pathogenetic accusation" of the active substance [1]. The creation by control bodies of a time interval within which pharmaceutical companies could self-test or "cleanse themselves" of nitrosamine-contaminated

batches could also be viewed as a kind of "indirect self-recognition of their pathogenetic role" [1,7,12]. So, too, could the creation of "protective regimes" for companies around the world and the parallel blocking of checks for the presence or absence of nitrosamines in certain geographical regions [12]. The first European study on the subject linked the use of sartans with a definite increased risk of developing melanoma - between 44% and 53%: both "long-term, low-intensity (OR 1.53; 1.05-2.23) and high-intensity (OR 1.44; 0.56-3.69) angiotensin receptor blocker use was associated with malignant melanoma" [4].

The aim of another, subsequent international retrospective study, presented formally as an American Academy of Dermatology (AAD) poster in Washington, DC in 2016, was to look again for an association (or risk) between the development of melanoma / basal cell carcinoma and the use of various antihypertensive drugs (figure 3) [5]. The results of this study clearly showed a doubling of the risk of developing melanoma after administration of angiotensin receptor blockers. (OR; 2.21; 95% confidence interval (CI): 1.45-3.36), (figure 3) [5]. The same study also found an approximately 36% risk of developing basal cell carcinomas after the use of angiotensin receptor blockers for arterial hypertension: (OR; 1.36; 95%, CI 1-1.83) (figure 3) [5]. In practice, there are international data on "simultaneous or parallel increased risk" of developing melanocytic and non-melanocytic skin tumors after administration of sartans, and there are clinical reports that fully correspond to those described in our patient (figure1,2) [4,5]. The role of angiotensin receptor blockers / sartans in nevus associated melanomas has also been the subject of discussion and serious observation in the medical literature [7,10]. The available data on the subject are indicative of the possible drug triggering of dysplastic nevi in the direction of melanoma after taking sartans as monotherapy or in combination with hydrochlorothiazide) [7,10].

3167

Association of melanoma and nonmelanoma skin cancer with antihypertensive drugs: A report from the Research on Adverse Drug events And Reports project

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Introduction: Some antihypertensive drugs may increase the risk of skin cancer, but findings are inconsistent regarding the possible association of exposure to these agents including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs) and thiazides (TZs) with occurrence of malignant melanoma (MM), basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). The aim of this study was to investigate further these possible associations.

Methods: The Northwestern Medicine Enterprise Data Warehouse repository was searched to detect patients, age 18-89 years, with two consecutive prescriptions for an ACEI, ARB or TZ. Subsequent diagnoses of MM, BCC or SCC occurring at least 2 months after exposure to one of these drugs were identified using ICD9 codes. The control population, from the same repository, consisted of non-antihypertensive drug-exposed individuals. Adjusted odds ratio was obtained using logistic regression analyses.

Results: Between Jan. 2010 and Feb. 2015, a total of 635,687 individuals with documented age, race and gender were detected. Of 5772 patients with prior exposure to an ARB: 25 MM, 45 BCC and 18 SCC were detected. Of 13,617 patients with prior exposure to an ACEI: 28 MM, 94 BCC and 35 SCC were detected. Of 5400 patients exposed to a TZ: 9 MM, 18 BCC and 13 SCC were detected. After adjusting for age, gender and race, a significant increased risk of melanoma was determined for ARBs (OR: 2.21; 95% CI: 1.45-3.36) and TZ (OR: 2.03; 95% CI: 1.04-3.92). An increased risk of basal cell carcinoma was determined for ARBs (OR: 1.36; 95% CI: 1-1.83) and ACEIs (OR: 1.31; 95% CI: 1.06-1.62). Finally, an increased risk of squamous cell carcinoma was determined for ARB, ACE and TZ (OR: 1.75; 95% CI: 1.08-2.8; OR: 1.59; 95% CI: 1.12-2.25; OR: 5.47; 95% CI: 1.99-6.04; respectively).

Conclusions: These findings serve to delineate the association of malignant melanoma and nonmelanoma skin cancer subsequent to ACEI, ARB and TZ exposure. This may have clinical relevance related to the choice of antihypertensive agent, particularly for patients with known risk factors for skin cancer. Given the widespread use of these drugs, increased pharmacovigilance, along with education for both patients and health practitioners, are warranted.

Commercial support: None identified.

Figure 3: Poster from AAD, Washington DC, 2016 [8].

Of interest are the subsequent observations of the same American group of researchers involved with the previously mentioned 2016 AAD poster, who after study of a significantly increased number of patients, found an even stronger association / risk of non-melanocytic skin tumors after use of angiotensin receptor blockers / sartans (depending on the applied statistics - between 2 to about three times increased risk for BCC: unadjusted OR (95% CI): 2,16 (1,85-2,52)/ adjusted OR (95%CI): 2,86 (2,13-3,83) [21], (figure4).

According to the data presented by colleagues, it is clear that in parallel with the risk of BCC, there is a risk of developing melanoma after the use of sartans; this risk is between 24% and more than 225% (depending on the used statistical methodology: adjusted / not adjusted) [21] (figure 4).

None of the presented studies comment on or exclude the most important factor for carcinogenesis: the nitrosamine contaminants [4,5,7,10,21]. The most serious problem in the group of patients taking angiotensin receptor blockers for the treatment of hypertension is the elucidation of the precise cause, or means by which carcinogenesis is triggered [1,7]. A particular problem is the lack of verification of a number of generic and original preparations on the pharmaceutical market as to whether or not they are affected by nitrosamine contamination; as a result, nitrosamines cannot be entirely excluded as generators of melanomas and basal cell carcinomas [1,7]. The available information leads to the conclusion that Nitrosamines are probably responsible for the potentiation of the neoplastic processes of various types of tumors in the human body [1,6].

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 (0.69)
Unexposed, *n* (%)	81,396 (75)	772 (0.95)	217 (0.27)	252 (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	2.15 (1.85–2.52)	2.50 (1.93–3.23)	2.25 (1.73–2.94)
Adjusted OR (95% CI)	1	2.85 (2.13–3.83)	2.22 (1.37–3.61)	1.24 (0.54–2.85)
Thiazides				
Exposed, *n* (%)	15,156 (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

Figures 4: Table regarding the possible risk of developing melanoma and nonmelanoma skin cancer regarding the data from Nardone B et al [9].

Conclusion

We have presented a rare case of a possible drug-induced high-risk epithelial tumor - basal cell carcinoma - near the eye, occurring in parallel with multiple eruptive, partly dysplastic nevi, following the administration of valsartan. For the first time in the world literature, the possible key role of nitrosamines as inducers of melanoma, melanoma precursors and non-melanocyte skin cancers is discussed. The data analysed in this scientific paper concern drugs that have not been checked as batches by control authorities for the presence or absence of nitrosamines. An innovative, unpublished scheme for the treatment of a non-melanoma skin tumor by immunocryotherapy has been applied, leading to complete remission.

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