Portuguese Journal of Dermatology and Venereology

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CASE REPORT

Giant BCC of the scalp after telmisartan/amlodipine: potential role of nitrosamine contamination as main cause for skin cancer development

CBC gigante do couro cabeludo após telmisartana/amlodipina: papel potencial da contaminação por nitrosamina como principal causa para o desenvolvimento de câncer de pele

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Abstract

The problem of drug-induced cancers, and in particular skin cancers after intake of various antihypertensive drugs, is increasing, but at the same time is gaining some clarity. In addition to melanocytic cancers, development of keratinocytic cancers is increased after the administration of sartans. It is believed that the procarcinogenic potential of the medication could be due to contamination of tablets with nitrosamines, which are known as mutagens. Regardless of the presence of angiotensin receptors in the skin and tumor tissue, the pharmacologic influence of the sartan is considered to be secondary and insignificant in relation to the processes of carcinogenesis. In certain cases, this influence is even defined as an antitumorous effect. We present a female patient who had been taking telmisartan/amlodipine 80/5 mg daily for 9 years and, after 4-5 years, developed a scalp tumor, confirmed histopathologically as a basal cell carcinoma (BCC) and treated successfully by surgical excision. The discussion is mainly focused on the potential role of nitrosamines as a new key player in the pathogenesis of keratinocytic cancers and BCC in particular.

Keywords: Nitrosamines. Basal cell carcinoma. Keratinocytic cancer. Dermatologic surgery. Telmisartan. Amlodipine.

Resumo

O problema dos cânceres induzidos por drogas, e em particular os cânceres de pele após a ingestão de vários medicamentos anti-hipertensivos, está aumentando, mas ao mesmo tempo está ganhando alguma clareza. Além dos cânceres melanocíticos, o desenvolvimento de cânceres queratinocíticos aumenta após a administração de sartans. Acredita-se que o potencial procarcinogênico do medicamento possa ser devido à contaminação dos comprimidos com nitrosaminas, conhecidas como mutagênicas. Independentemente da presença de receptores de angiotensina na pele e no tecido tumoral, a influência farmacológica do sartan é considerada secundária e insignificante em relação aos processos de carcinogênese. Em certos casos, essa influência é até definida como um efeito antitumoral. Apresentamos uma paciente que fazia uso diário de

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Received: 13-01-2023
Accepted: 06-03-2023
DOI: 10.24875/PJDV.23000001

Available online: 17-03-2023
Port J Dermatol and Venereol. 2023;81(3):217-219
www.portuguesejournalofdermatology.com

telmisartan/amlodipina 80/5 mg por 9 anos e após 4-5 anos desenvolveu um tumor no couro cabeludo, confirmado histopatologicamente como um carcinoma basocelular (CBC) e tratado com sucesso por excisão cirúrgica. A discussão está focada principalmente no papel potencial das nitrosaminas como um novo ator-chave na patogênese dos cânceres queratinocíticos e do CBC em particular.

Palavras-chave: Nitrosaminas. Basalioma cancro cutâneo. Tumor queratinocitico. Cirurgia dermatológica. Telmisartan. Amlodipina.

Introduction

Systemic treatments with sartans, and in particular telmisartan, are generally associated with a more frequent association with all forms of human cancer[1]. According to other scientific works, this risk is determined by the total cumulative intake of sartans over a certain period of time[2].

Literature data has linked both keratinocytic and melanocytic cancers to the use of sartans[3].

The simultaneous occurrence of basal cell carcinomas (BCC) and dysplastic nevi after taking sartans or sartans in combination with hydrochlorothiazide could be consideredas extremely important, eventually confirmatory, regarding the thesis that potential contamination with nitrosamines is able to generate multiple forms of cancer or skin cancer and/or its precursors[4,5]. Contamination with mutagenic nitrosamine remains the link between the intake of sartans and the development of skin cancer. The recently confirmed presence of nitrosamines in hydrochlorothiazide (within monomedication or in combination), could reinforce the mentioned assumptions[6].

Case report

A 69-year-old female came to the dermatology department with a 5-year-old tumor formation on the scalp in close proximity to the frontal region, that had been growing for about five years prior to the consultation. Physical examination showed a giant tumor, 5-7 cm in diameter, covered with hemorrhagic crusts, with undefined borders (Fig. 1A). A biopsy taken preoperatively confirmed the histophatological diagnosis of basal cell carcinoma.

Due to comorbidities (arterial hypertension known for 13 years, hypertriglyceridemia, hypercholesterolemia and sinus tachycardia) the patient was under systemic therapy with Telmisartan 80 mg/Amlodipine 5 mg once daily for 9 years, Hydroxyzine 25 mg once daily in the evening and Chlorthalidone 25 mg once daily for 2 years. Glucose level was 7.15 mmol/L (normal range 3.9-5.6 mmol/L), but other blood tests were normal. A Computerized Tomography of the head showed a normal brain image without deviations or changes in the bone structure of the frontal bone.

After consultation with a cardiologist, the medication was switched to moxonidine 0.2 mg twice daily, Nebivolol 2.5 mg once daily, and clonidine when needed.

The tumor was excised under general anesthesia followed by reconstruction with an advancement rotation flap. Histopathology showed a stage 2 (T2N0M0) nodular type of basal cell carcinoma without evidence of metastases. There was a good cosmetic result, and outpatient follow-up showed no tumor recurrence (Fig. 1B,C).

Discussion

Nitrosamines are well-known mutagens, carcinogens that without any doubt are causing in vivo different types of carcinomas such as: cancers of the bladder, lung, stomach, leukaemia, multiple myeloma, oesophagus, prostate, pancreas and liver[7]. Their pathogenetic role in the development of almost all forms of cancer remains undeniable and well-defined[1,2,7], either after inhalation[8] or oral intake should. Their procarcinogenic effect remains statistically significant after taking sartans potentially contaminated with nitrosamines, especially for keratinocyte cancer, confirmed in serious retrospective analyses: unadjusted OR (95% CI) for BCC: 2.16 (1.85-2.82), as well as adjusted OR (95% CI) for BCC: 2.86 (2.13-3.83)[8].

A two-fold increased expression of the Angiotensinogen gene in tumor cells of patients with BCC has been shown[9]. Although the role of the reninangiotensin system in the skin physiology is undeniable[10], it remains unclear whether this expression is a result or a cause for the development of BCC.

A number of publications have established a link between sartans administration and the increased risk for melanoma progression in the experimental environment[11,12]. An interesting recent publication indicated that valsartan contaminated with nitrosamines was associated with a 10% higher risk of developing melanomas[13]. Regarding BCC, such observations are

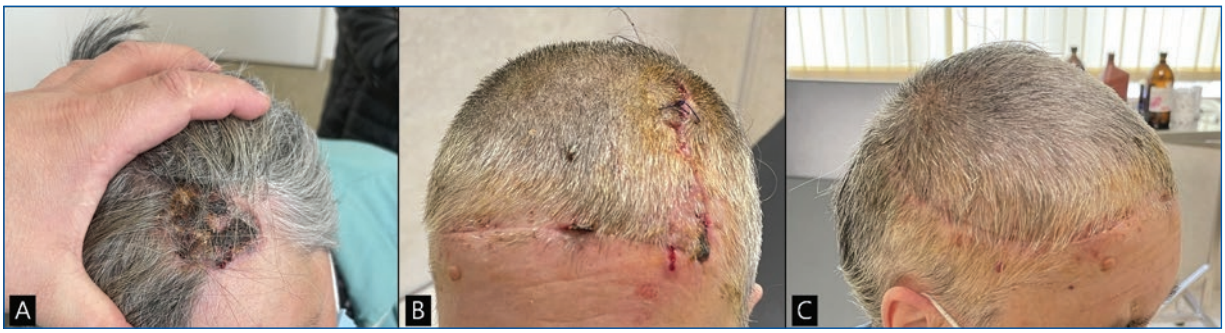

Figure 1. A-C: giant tumor formation of the scalp, 5/7 cm in size, covered with hemorrhagic crusts, with undefined borders (a). Outpatient follow-up with primarly healing wound and good aesthetic outcome (b,c).

completely absent, but the present case will perhaps be accompanied by other reports in the future. Currently, sartan use is associated with a significantly increased risk of actinic keratoses development, which are perceived as preforms of keratinocyte cancer[14].

According to expert conclusions of specialised collectives, which are focused on monitoring the possible side effects of nitrosamines, their potential availability in sartans, ACE inhibitors, thiazide diuretics, metformin, and ranitidine, could lead to skin cancer development[15].

The potential role of nitrosamines is mentioned within the perspective of large-scaled retrospective analyses[8]. According to them, both sartans and thiazide diuretics, but also ACE inhibitors, are associated with an over two-fold to nearly three-fold increased risk of developing BCC[8]. Batches of all these three classes of medications have been withdrawn from distribution in recent years due to the elevated concentrations of nitrosamines, many times exceeding the so-called ADIs (Acceptable daily intake doses).

Following statistical results and analyses[8], it remains unlikely that the link between the three types of skin cancers (BCCs, Squamous cell carcinomas and melanomas) and different classes of antihypertensive medication with distinct pharmacologic activities is sporadic, but very probably related to common nitrosamine contamination of all these classes of drugs[8].

In this case report, the absence of painful sunburns in the patient's history, as well as the long-term use of telmisartan (potentially contaminated with nitrosamines), reinforce this pathogenetic relationship.

Funding

None.

Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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