CASE REPORT

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MELANOMA IN SITU AND PHOTOTOXIC DRUG REACTION APPEARING SIMULTANEOUSLY AFTER ANTIHYPERTENSIVES INTAKE: PHOTO NITROSO CARCINOGENICITY OF DRUGS AS POSSIBLE RISK FACTOR FOR THE DEVELOPMENT AND PROGRESSION OF CUTANEOUS MELANOMA

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Abstract. *Drug-mediated nitrosogenesis or oncopharmacogenesis of skin cancer in general and melanoma skin cancer development in particular could be pathogenetically determined/ explained by the presence of photocarcinogens in drugs. These photocarcinogens are also known as nitrosamines. A number of studies in the scientific literature have linked the intake of antihypertensive drugs from heterogeneous groups to the generation of phototoxicity and the subsequent development of cutaneous melanomas. However, these particular groups of antihypertensive drugs belong at the same time to those declared by regulatory authorities worldwide (FDA/EMA) as affected by contamination with photocarcinogens. According to the most recent literature, 1) the number of potentially nitrosamine-contaminated antihypertensive drugs taken and 2) exposure to ultraviolet radiation could correspond to the severity of the clinical picture. We report a patient who developed a phototoxic reaction and melanoma in situ in the context of a relatively short-term use of the four types of antihypertensive drugs: lisinopril/ amlodipine, followed by valsartan/ hydrochlorothiazide. An analysis of the possible pathogenetic association is made, discussing recent literature concepts such as: drug-induced photo nitrosogenesis / carcinogenesis of cutaneous melanoma.*

Key words: *nitrosamines, drug related photoxicity, photocarcinogenicity, melanoma, telmisartan, hydrochlorothiazide, lisnopril, amlodipine, clinical case report*

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INTRODUCTION

The concept of drug-induced carcinogenesis – particularly in relation to skin cancer, has gained increasing attention in recent years [1, 2]. The mechanisms of photosensitivity and photocarcinogenicity are fundamental to the development of skin cancer and play a central role in its pathogenesis [3].

Nitrosamines are well-established mutagenic compounds that, over the years, have demonstrated

genotoxic properties and the ability to mediate phototoxicity [3] and photocarcinogenicity in humans [4]. In the context of polymorbidity and polypharmacy, their presence raises significant health concerns – particularly the risk of cancer, including skin cancer: melanoma and non-melanoma skin cancer [5, 6].

Contamination of pharmaceuticals with nitrosamines is a serious challenge for both the regulatory authorities and manufacturers [7, 8].

Although acceptable daily intake limits have been established for these carcinogenic [8], mutagenic, and genotoxic substances, they have also been identified as phototoxic substances because of the instability of the nitroso group under UV light [3, 9, 10].

The photomutagenicity and photogenotoxicity of seven N-dialkylnitrosamines were demonstrated in Ames bacteria (S. typhimurium TA1535) under simultaneous UVA exposure, in the absence of metabolic activation [10]. Mutagenicity of pre-irradiated N-dialkylnitrosamines were also observed in S. typhimurium (hisG46, TA102 and YG7108) without metabolic activation [10]. It is suggested that UVA photons are absorbed by the N-nitroso groups in these compounds, leading to photolysis and the release of nitric oxide [10]. This, in turn, triggers the formation of reactive oxygen species, initiating a chain-like reaction – including DNA strand breaks and subsequent DNA damage – that result in mutations [10].

The phototoxicity of nitrosamines is a non-specific property resulting from the photodecomposition of the nitroso group under sunlight [9, 10]. Their additional genotoxicity can be viewed as a compounding hazard and real danger for humans [11, 12].

Telmisartan, hydrochlorothiazide, amlodipine, and lisinopril are medications currently listed by the FDA as being contaminated with nitrosamines [7, 8,]. These drugs are also known to be phototoxic, with their use linked to the development of skin cancers in UV-exposed areas [13, 14] – and, notably, to melanomas in particular [14, 15].

We present a case of a patient who simultaneously developed a drug-induced eruption and melanoma during treatment with telmisartan and hydrochlorothiazide. This case highlights the emerging concept of skin cancer involving phototoxicity, photocarcinogenicity, and nitroso photo carcinogenesis.

CLINICAL CASE DESCRIPTION

A 54-year-old male patient presented to the dermatology department due to a primary complaint of a relatively small pigmented formation on the back that had been present for approximately one year (Fig. 1a). Over the past six months, the patient noticed changes in shape and doubling in the size of the lesion. Additionally, he reported the onset of a widespread, intensely pruritic rash on the whole body that began approximately two weeks prior to the consultation (Figs 1a, 1b).

The patient is diagnosed with arterial hypertension, for which he had been taking telmisartan/hydrochlorothiazide 80 mg/12.5 mg once daily in the morning and atorvastatin 20 mg once in the evening, both

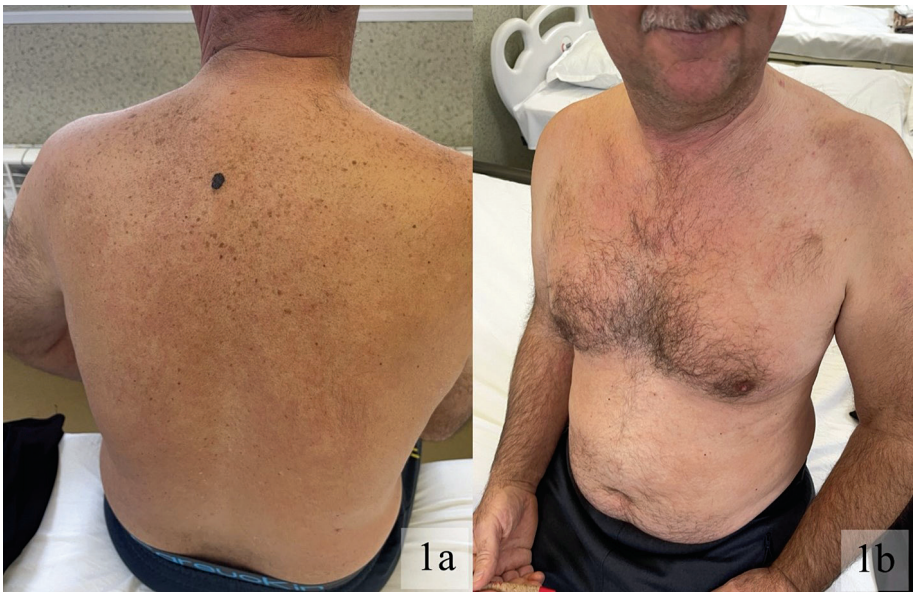

Fig. 1 a, b. A pigmented lesion located on the back, measuring 1 cm by 2 cm, with irregular borders (a). Additionally, a widespread erythema-infiltrative exanthem is observed on the truncus – anterior (a) and posterior views (b)

therapies started one month prior to the consultation. He had also been taking moxonidine 0.2 mg once daily for the past year. Six months earlier, the patient underwent treatment with lisinopril/amlodipine 10 mg/5 mg, but the therapy was discontinued after 6 months due to an allergic / phototoxic reaction.

Dermatological examination revealed a pigmented lesion located on the back, measuring 1 cm by 2 cm, with irregular borders (Fig. 1a). Additionally, a widespread drug-induced exanthem was observed on the truncus (Fig. 1a, b). No enlarged lymph nodes were palpable.

Routine laboratory tests showed slight abnormalities, including PDW 10.5% (normal range 11-15%), urine specific gravity test 1.030 mmol/L (1.010-1.025 mmol/l), and GGT 60.0 U/L (0-55 U/L). A CT scan identified a parenchymal lesion in the right lung, for which follow-up in 3-6 months was recommended. Additional findings included pulmonary fibrotic changes, bilateral subpleural changes in the lower lobes; and hepatic cysts, all of which were sized less than 5 mm.

Given the suspicion of drug-induced phototoxic dermatitis, a cardiology consultation was conducted, and the potential triggering medications were discontinued or replaced. The patient's medication was adjusted to amlodipine 5 mg taken twice daily (morning and evening), moxonidine 0.3 mg twice daily (morning and evening), and atorvastatin 20 mg once daily in the evening.

Treatment for dermatitis was initiated with loratadin 5 mg, methylprednisolone 16 mg i.v. for 3 days, followed by 8 mg i.v., famotidine 80 mg and topical clobetasol propionate. A punch biopsy of the rash was performed revealing moderate ortho- and follicular hyperkeratosis, uniform acanthosis, focal vacuolar degeneration of basal keratinocyte row, sparse perivascular round cell inflammatory infiltrate in the upper dermis, with single extravasated eosinophils in the upper dermal compartment. The histological picture was consistent with drug-induced dermatitis.

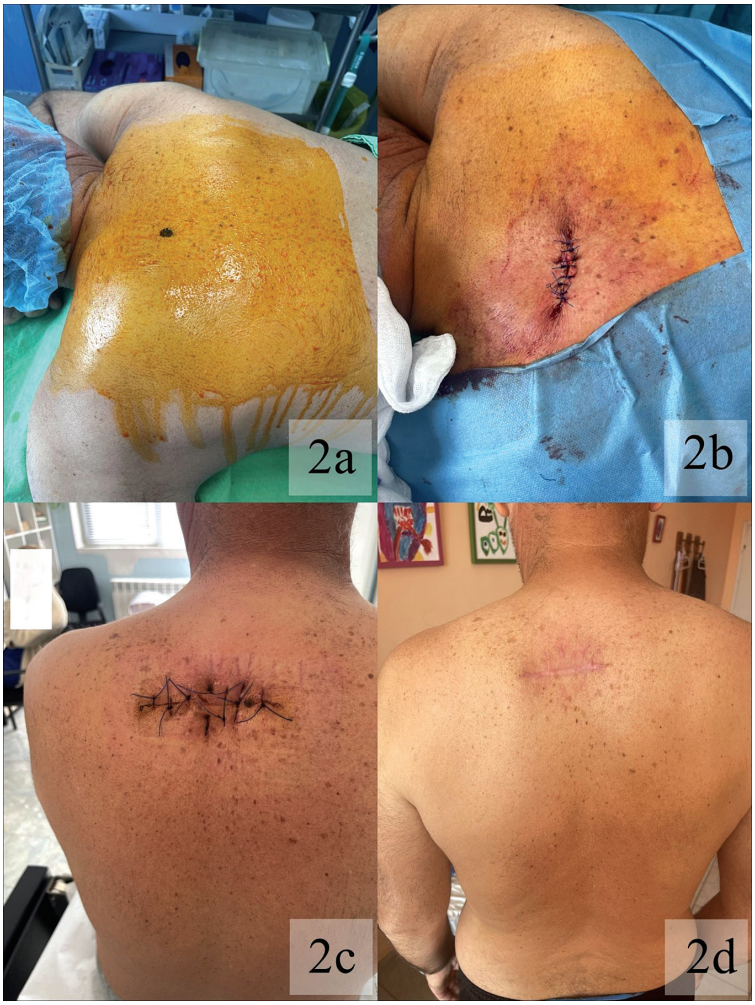

Fig. 2 a-d. The pigmented lesion on the back was preoperatively marked (a) and surgically removed with an elliptical excision, with surgical margins of 0.3 mm. The skin edges were adapted with single skin sutures (b). The postoperative suture removal was performed on the 7th day (c) and the 7th day (d)

For the pigmented lesion on the back, suspicious clinically and dermatoscopically for thin melanoma or melanoma in situ, an elliptical excision was performed under local anesthesia with 2% lidocaine, with surgical margins of 0.3 mm. The skin edges were adapted with single skin sutures (Fig. 2a-c). Postoperative complications were not observed (Fig. 2d). Histopathological examination revealed an extensive, asymmetric, poorly demarcated melanocytic lesion, represented by ortho- and follicular hyperkeratosis, irregular acanthosis, proliferation of atypical large fusiform melanocytes, forming nests of various diameter, obscuring the dermo-epidermal boundary, and consuming the overlying epidermis, demarcated by fibroplastic, lichenoid lympho-plasmacytic stroma with many melanophages and foci with regression. There was suspected folliculotropic invasion of the papillary dermis to a depth of 0.26 mm. Resection margins were clear. The histological picture corresponded to melanoma in situ with a suspicious focus in the papillary dermis to a depth of 0.26 mm.

Re-excision was performed with margins of 0.7 mm. The materials were sent for histological verification, which showed no evidence of melanoma infiltration.

Due to the uncertainty of the CT scan, the following was recommended: 1) BRAF testing from primary/ lesional tumor tissue, and 2) PET scan to clarify the dignity of the lesion in the lung. Regarding the drug-induced exanthema allergology consultation and testing for hypersensitivity/ phototoxicity to ACE inhibitors and ARBs were advised. Continued treatment with methylprednisolone 4 mg in a tapering schedule and loratadine 5 mg was recommended.

Later the patient underwent a PET scan, which reported no abnormal findings.

DISCUSSION

With respect to skin cancer pathogenesis, concepts such as phototoxicity and subsequent photocarcinogenicity remain key, particularly in the context of the mono- or polydrug administration [16]. The nitrosamines in drugs (but not only) appear to be by their very characterization precisely the main candidates/ "materially and/or morally responsible parties" in terms of the above-mentioned properties, as potential essential cofactors also for the pathogenesis of skin cancer and melanoma in particular [17].

The combination of sartans and hydrochlorothiazide is associated with 2 important facts: 1) in principle, either of the two preparations could be affected by nitroso contamination, and 2) after taking this combination medication, cutaneous melanomas also occur [17-20]. The association between the intake of nitrosamine-contaminated drug products containing sartans and the generation of melanomas has also been confirmed in the observation of larger groups of patients [21].

The same is true when monitoring patients taking hydrochlorothiazide: the risk of developing melanocytic and keratinocytic skin cancer remains present [14]. Hydrochlorothiazide was recently declared by the IARC [22] to be carcinogenic to humans due to its phototoxicity. This conclusion was reached after an in-depth analysis of clinicopathological and epidemiological data, which are strongly suggestive of a risk of developing (mainly) spinocellular carcinomas (after hydrochlorothiazide intake), but also a definite association, albeit limited, between the intake of the drug hydrochlorothiazide and the subsequent occurrence of cutaneous melanomas was found [22]. This publication in Lancet Oncology does not specify 1) what determines phototoxicity and 2) whether the medication contained photocarcinogens, also known as nitrosamines [23].

The medication found based on the history in the patient we described (at the time of his admission) consisted precisely of the combination of sartan with hydrochlorothiazide, and in the context of this admission he developed toxic exanthem and melanoma in situ. The intake of this medication is about a month old. The patient's prior medication includes a combination product containing the ACE inhibitor lisinopril and the calcium antagonist amlodipine from – 6 months ago or prior to taking telmisartan/hydrochlorothiazide.

The risk of melanomas after taking ACE inhibitors based on their phototoxicity is not new to the academic community [24, 25]. Similar data are available on the development of cutaneous melanomas in the context of potential nitrosamine-contaminated polydrug antihypertensive use of: amlodipine, valsartan and hydrochlorothiazide [27]. The intake of a cocktail of photocarcinogens, also known as nitrosamines, has been shown to be extremely risky with respect to the development of skin cancer and cutaneous melanomas in particular [4, 17, 21, 27], but not only [28-31].

CONCLUSIONS

Future regulatory policies should pay serious attention to these circumstances with a view to eliminating the so-called photocarcinogens/nitrosamines from drugs worldwide because of their possible etiopathological role for the skin cancer and cutaneous melanomas development and progression.

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Consent for publication: *Consent form for publication was signed by the patient and collected.*

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