

**КЛИНИЧНИ СЛУЧАИ
CASE REPORTS**

**FIRST CASE IN THE WORLD LITERATURE OF MUSHROOM-LIKE
ACHROMATIC PEDUNCULATED MELANOMA ON THE BACK AFTER INTAKE
OF (NITROSO) TAMSULOSIN: PHOTOCARCINOGENICITY TRIGGERED DUE
NITROSAMINE CONTAMINATION IN DRUGS AS COFACTOR
FOR MELANOMA PATHOGENESIS**

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**ПЪРВИ СЛУЧАЙ В СВЕТОВНАТА ЛИТЕРАТУРА
НА ГЪБОПОДОБЕН АХРОМАТИЧЕН ПЕДУНКУЛИРАН МЕЛАНОМ НА ГЪРБА
СЛЕД ПРИЕМ НА (НИТРОЗО) ТАМСУЛОЗИН: ФОТОКАРЦИНОГЕННОСТ,
ПРЕДИЗВИКАНА ОТ ЗАМЪРСЯВАНЕ С НИТРОЗАМИНИ В ЛЕКАРСТВАТА
КАТО КОФАКТОР ЗА ПАТОГЕНЕЗТА НА МЕЛАНОМА**

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Abstract:

Drug-mediated phototoxicity and subsequent photocarcinogenicity are concepts or phenomena that, until recently, remained largely ignored, and the risk of their presence and their association with skin cancer generation, was underestimated. A number of publications in the world literature have associated the intake of heterogeneous classes of drugs with the development of photocarcinogenic effects, and hence the generation of melanomas (but also keratinocytic cancers) in particular. Other publications again find a link between the intake of heterogeneous types of systemic medication, the contamination of the drugs with photocarcinogens (also known as nitrosamines), and the subsequent development of cutaneous melanomas. In this context, we present the first case of achromatic, pedunculated, mushroom-like melanoma arising after intake of potentially photocarcinogen/nitrosamine-contaminated tamsulosin. The discussion focuses on drug mediated nitrosogenesis/photocarcinogenesis, concerning phototoxicity or the photo decomposition of the nitroso group under UV light.

Key words:

nitroso tamsulosin, achromatic pedunculated mushroom-like melanoma, drug-related phototoxicity, photo nitrosocarcinogenicity

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Резюме:	Фототоксичността, предизвикана от лекарства, и последващата фотокарциногенност са концепции или явления, които доскоро оставаха до голяма степен игнорирани, а рискът от тяхното наличие и връзката им с появата на рак на кожата се подценяваше. Редица публикации в световната литература свързват приемането на хетерогенни класове лекарства с развитието на фотокарциногенни ефекти и оттам с появата на меланоми (но също така и на кератиноцитни ракови заболявания) в частност. Други публикации отново установяват връзка между приемането на хетерогенни видове системни лекарства, замърсяването на лекарствата с фотокарциногени (известни също като нитрозамини) и последващото развитие на кожни меланоми. В този контекст представяме първия случай на ахроматичен, педункулиран, гъбоподобен меланом, възникнал след приемане на потенциално фотокарциногенен/замърсен с нитрозамини тамсулозин. Дискусията се фокусира върху медираната от лекарства нитрозогенеза/фотонитрозокарциногенеза, свързана с фототоксичността или фоторазграждането на нитрозогрупата под въздействието на ултравиолетова светлина.
Ключови думи:	нитрозотамсулозин, ахроматичен педункулиран гъбоподобен меланом, лекарствена фототоксичност, фотонитрозокарциногенност
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INTRODUCTION

Mushroom-like cutaneous tumors are a rare phenomenon, with cutaneous melanoma being one of the skin cancers that can present with such clinical appearance, alongside tumors like Merkel cell carcinoma and basal cell carcinoma [1]. Regardless of the diagnosis, surgical excision remains the primary approach in the treatment of these conditions [2].

Achromatic pedunculated mushroom-like melanomas could arise on the basis of preexisting melanocytic lesions, such as medium-sized or giant nevi [3, 4], and in these cases they also are associated generally with a significantly poorer prognosis. However, these tumors could also arise on a completely intact skin surface [1].

The fact that these melanomas arise on the basis of previous and somewhat risky lesions, such as congenital melanocytic nevi (medium- and giant-sized), is indicative of the fact that in all likelihood something has been able to trigger this progression. According to the most recent literature, drug-mediated phototoxicity/photocarcinogenicity could be one of the factors that until recently were seriously underestimated and overlooked with regard to the development of skin cancer and melanoma in particular [5].

The fact that structurally fundamentally different classes of drugs generate phototoxicity and carcinogenicity [5] remains indicative of one thing: the detection, identification and potential elimination of this unifying factor should become a priority for scientists and clinicians worldwide.

We present a case of a giant, mushroom-like achromatic polypoid melanoma on the back, developed following long-term oral intake of potentially nitrosamine-contaminated tamsulosin. The possibility of drug-induced melanoma, with tamsulosin emerging as a potential contributing factor, is explored in this context.

CLINICAL CASE DESCRIPTION

An 81-year-old male patient presented to the dermatology department with a tumorous lesion located on the back. According to the patient's wife, the lesion had previously appeared as a nevus and had significantly increased in size over the past six months.

The patient's medical history included non-insulin-dependent type 2 diabetes mellitus diagnosed in 2015, benign prostatic hyperplasia since 2017, stroke, vascular dementia since 2022, as well as hypercholesterolemia and hyperlipidemia. His long-term systemic therapy consisted of glimepiride 4 mg (half a tablet twice daily, morning and evening for 10 years), dapagliflozin 10 mg once daily (for 8 years), tamsulosin hydrochloride 0.4 mg once in the evening (since 2017), piracetam 1200 mg once daily (since 2022), nicergoline three times a day (since 2022), donepezil hydrochloride 5 mg twice daily (at noon, and in the evening, since 2022), memantine hydrochloride 10 mg once in the morning (since 2022), and vinpocentin twice daily (morning and at noon, since 2022).

Routine blood tests revealed the following abnormalities: elevated PDW 16.5% (11-15%), low lympho-

cytes 14.9% (20-40%), elevated granulocytes $7.94 \cdot 10^9/l$ ($2.0-7.8 \cdot 10^9/l$), elevated ESR 26 mm/h (0-20 mm/h), elevated cholesterol 6.12 mmol/l (3.5-6.0 mmol/l), elevated LDL 3.7 mmol/l (1.5-3.0 mmol/l), elevated triglycerides 2.68 mmol/l (0.08-1.7 mmol/l), elevated glucose levels at 6.86 mmol/l (3.8-6.1 mmol/l), and elevated LDH levels 404.0 U/l (140-280 U/L).

Dermatological examination revealed a 6 x 6 cm pedunculated, erythematous-ulcerative tumor, covered in places with crusts, located on the back. The clinical suspicion for a mushroom-like achromatic cutaneous melanoma (polypoid type) was aroused, with basal cell carcinoma considered as a differential diagnosis.

Surgical excision under general endotracheal anesthesia was planned. Due to episodes of aggression, preoperative consultations with a cardiologist, anesthesiologist, and psychiatrist were conducted. Sedation with quetiapine 25 mg (half a tablet twice daily – mornings and evenings) was prescribed starting on the day before the surgery. The evening dose was skipped preoperatively and resumed on the day after the surgery. Piracetam was discontinued.

On the day of the surgery, due to the patient's aggression, the procedure was performed under short-

term intravenous anesthesia. The lesion was removed with an elliptical excision with surgical safety margin of 1 cm in all directions. The wound defect was then closed with one Donati suture and multiple simple interrupted sutures. Histopathological analysis revealed an extensive polypoid melanocytic lesion, characterized by superficial epidermal necrosis and compact proliferation of large melanocytes with marked pleomorphism, large nuclei with 1-2 nucleoli, and light cytoplasm, forming areas of artificial acantholysis, atypical necrosis and necrotic fields infiltrating the entire volume of the dermis. Immunohistochemical staining showed Sox-10 positivity in 70% of the tumor population. A high mitotic index and ulceration were noted. Breslow thickness was > 4 mm. Resection lines were clear. The histological picture corresponded to achromatic mushroom-like polypoid melanoma, staged as T4b Nx Mx.

A chest radiograph was performed due to a suspected dissemination of the process. No pathological findings were noted.

Further recommendations included a wide local re-excision with an additional 1 cm surgical safety margin, sentinel lymph node biopsy, PET-CT scan, and evaluation of S-100 protein levels.

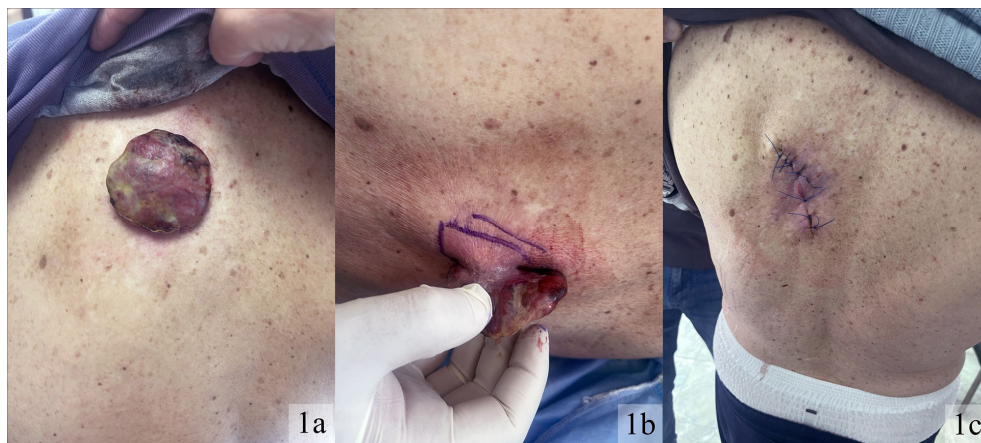


Fig. 1. Clinical picture: achromatic mushroom like melanoma. 1a: Pedunculated, erythematous-ulcerative tumor, measured 6 cm x 6 cm, covered in places with crusts, located on the back; 1b: Preoperative markings: pedunculated mushroom-like achromatic cutaneous tumor, viewed from above; 1c: Post-operative day 7

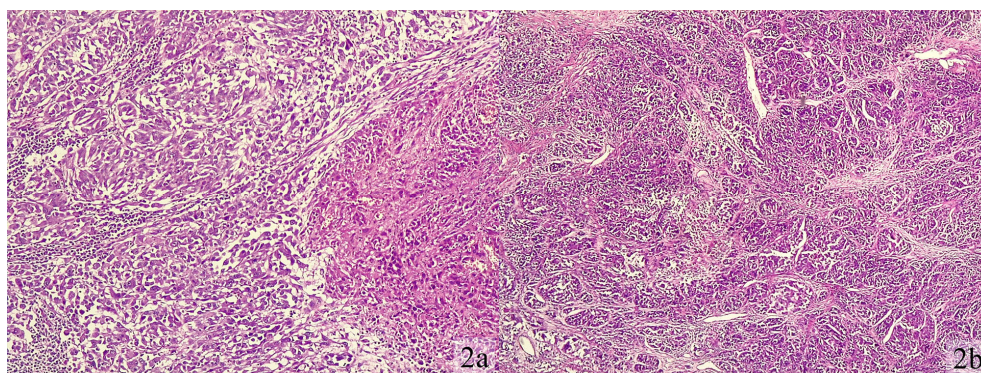


Fig. 2. Histology panel. 2a: Dyscohesive atypical melanocytes, intermingled with necrotic areas; 2b: Polypoid melanoma x large atypical melanocytes, forming dyscohesive nests, deeply penetrating the dermis

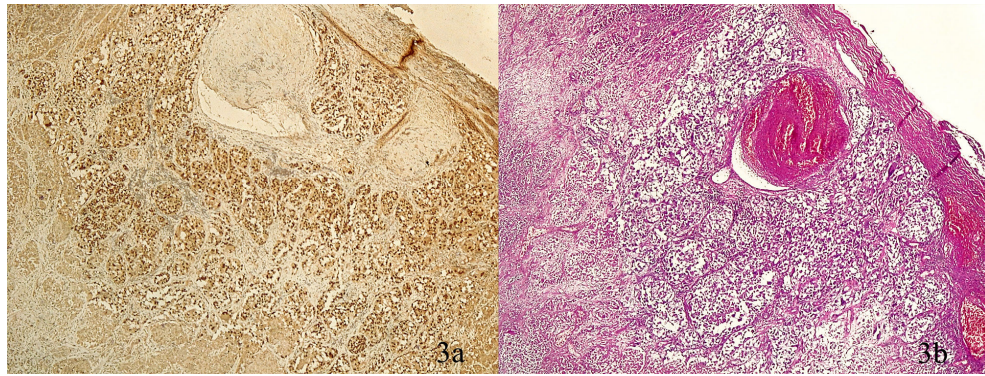


Fig. 3. Histology panel. 3a: Polypoid achromatic melanoma x Sox-10 x 40; 3b: Ulcerative polypoid achromatic melanoma x 40 x H&E

DISCUSSION

Available scientific data worldwide link nitrosamines to the phototoxicity generation [6], and hence, thanks to the cumulative effect over time, also to the generation of photocarcinogenicity in the context of a single or combined (potentially contaminated) drug intake in humans [7, 8]. In practice nitrosamines are photocarcinogens [9]. This property also appears to be completely independent of their pure carcinogenic potency [6] and is due to the tendency of their nitroso group to be unstable under the influence of sunlight [6, 10, 11].

In support of this fact is precisely the fact that drugs of relatively low carcinogenic potency (say, 4) [12], such as hydrochlorothiazide [12], are associated with cancer generation in humans [13]. The aforementioned drug has been declared as carcinogenic to humans by the International Agency for Research on Cancer (IARC) in terms of skin cancer development due to generation of photosensitivity/phototoxicity and subsequent photocarcinogenicity [14].

In practice, the phototoxicity/photocarcinogenicity in these cases could be determined by the so-called photocarcinogenicity of nitrosamines [6, 8, 9], which in certain of their representatives could also be supported by their pure, additional carcinogenicity or genotoxicity [12]. Over time, the effects of phototoxicity/solar radiation are likely to cumulate and could contribute to photocarcinogenicity with respect to melanomas but also to skin cancer in general [5, 15, 16]. In the presence of the intake of several drugs that contain photocarcinogens/nitrosamines, this phototoxicity effect could be amplified and lead more rapidly to the generation of a malignant cell clone or several such clones simultaneously [17, 18].

Similar pathogenetically based associations could be applied to the drug tamsulosin, which, according to the FDA list, belongs to the drugs potentially con-

taminated with photocarcinogens [12]. This particular drug has also been associated with the subsequent development of keratinocyte skin cancer based on its potential/actual phototoxicity [19, 20].

Starting from the circumstances involving 1) the overlap of the medication (tamsulosin) taken by our patient with the medication (again tamsulosin), which is officially included in the FDA list of photocarcinogen-contaminated drugs [12], and 2) the fact that in practice also other analogous observations draw attention to the subsequent development of skin cancer after taking tamsulosin [19, 20], analogously to the example of other drugs possessing an absolutely identical carcinogenic potency (hydrochlorothiazide in this case) [13, 14], it should be concluded that:

1) Drug-mediated photo nitrosogenesis of skin cancer and melanomas in particular should not be regarded as a myth, but rather as a reality.

2) A distinction should be made between the pure carcinogenic potency and the photocarcinogenic potency of photocarcinogens or the so-called nitrosamines in drugs.

3) Photocarcinogens can be considered as an important cofactor for the generation of melanomas and their rare forms such as achromatic pedunculated mushroom-like melanoma.

References

1. Wollina U, Langer D, Tchernev G. Mushroom-Like Skin Tumours: Report of Three Cases. *Open Access Maced J Med Sci*. 2017 Jul 21;5(4):515-517. doi: 10.3889/oamjms.2017.109.2
2. Heistein JB, Acharya U, Mukkamalla SKR. Malignant Melanoma. 2024 Feb 17. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2025 Jan.
3. Tchernev G. One Step Melanoma Surgery for Patient with Thick Primary Melanomas: "To Break the Rules, You Must First Master Them!". *Open Access Maced J Med Sci*. 2018 Feb 9;6(2):367-371. doi: 10.3889/oamjms.2018.084.
4. Tchernev G, Patterson JW, Bakardzhiev I, et al. Late Onset Achromatic Melanoma Arising in a Giant Congenital Mel-

- anocytic Nevus. Open Access Maced J Med Sci. 2017 Jul 18;5(4):533-534. doi: 10.3889/oamjms.2017.077.
5. Davis AE, Kennelley GE, Amaye-Obu T, et al. The phenomenon of phototoxicity and long-term risks of commonly prescribed and structurally diverse drugs. J Photochem Photobiol. 2024 Feb;19:100221. doi: 10.1016/j.jpap.2023.100221.
 6. Nishie K, Norred WP, Wasserman A, Keyl AC. Phototoxicity and differential hepatotoxicity as biological indicators of nitrosamine activity. Toxicol Appl Pharmacol. 1972 Dec;23(4):680-91. doi: 10.1016/0041-008x(72)90108-1.
 7. Tchernev G, Broshtilova V, Kordeva S. Innovations in dermatologic surgery and melanoma pathogenesis: from the personalised surgery to the concept of genomic mapping/targeting via nitrosamines in drugs: spotlight on contamination of angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Georgian Med News. 2025 Jan;(358):40-46.
 8. Tchernev G, Broshtilova V. (NDMA) Metformin and (NTTP) sitagliptin induced cutaneous melanomas: links to nitrosogenesis, nitroso-photocarcinogenesis, oncopharmacogenesis and the metabolic reprogramming. Georgian Med News. 2024 Mar;(348):132-143.
 9. Tchernev G, Broshtilova V, Kordeva S. Shark pedicle island flap for basal cell carcinoma of the perialar zone of the nose: phototoxicity and photocarcinogenicity mediated by potentially nitrosamine contaminated drug intake -a new explanation for the skin cancers pathogenesis? Georgian Med News. 2024 Jul-Aug;(352-353):218-222.
 10. Polo J, Chow YL. Efficient photolytic degradation of nitrosamines. J Natl Cancer Inst. 1976 May;56(5):997-1001. doi: 10.1093/jnci/56.5.997.
 11. Fan J, Deng C, Rao Y. Photodegradation of N-nitrosodimethylamine under 365 nm Light Emitting Diode Irradiation. Water Environ Res. 2022 Sep;94(9):e10787. doi: 10.1002/wer.10787.
 12. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cder-nitrosamine-impurity-acceptable-intake-limits>
 13. Cogliano VJ, Corsini E, Fournier A, et al. Carcinogenicity of hydrochlorothiazide, voriconazole, and tacrolimus. Lancet Oncol. 2025 Jan;26(1):15-16. doi: 10.1016/S1470-2045(24)00685-5.
 14. <https://www.iarc.who.int/featured-news/iarc-monographs-evaluation-of-the-carcinogenicity-of-hydrochlorothiazide-voriconazole-and-tacrolimus/>
 15. Dennis LK. Cumulative Sun Exposure and Melanoma in a Population-Based Case-Control Study: Does Sun Sensitivity Matter? Cancers (Basel). 2022 Feb 16;14(4):1008. doi: 10.3390/cancers14041008.
 16. Tatalovich Z, Wilson JP, Mack T, et al. The objective assessment of lifetime cumulative ultraviolet exposure for determining melanoma risk. J Photochem Photobiol B. 2006 Dec 1;85(3):198-204. doi: 10.1016/j.jphotobiol.2006.08.002.
 17. Tchernev G, Temelkova I. Valsartan Induced Melanoma?! First Description in Medical Literature! Open Access Maced J Med Sci. 2018 Dec 18;6(12):2378-2380. doi: 10.3889/oamjms.2018.517.
 18. Tchernev G. Nitrosogenesis of cutaneous melanoma: simultaneously development of primary cutaneous thick melanoma of the breast, thin melanoma/dysplastic mole of the back during parallel intake of bisoprolol, amlodipine and valsartan/ HCT: nitrosamine polycontamination in the multimедication as the most powerful skin cancer trigger. Georgian Med News. 2023 Jun;(339):83-88.
 19. Tchernev G, Kordeva S, Kirilova H, et al. Polypharmacy and cancer: a new vision for skin cancer pathogenesis-phototoxicity and photocarcinogenicity due to nitrosamine contamination during telmisartan/ tamsulosin intake. Georgian Med News. 2024 Nov;(356):89-93.
 20. Tchernev G, Todorov I, Ivanov L, Kordeva S. Basal cell carcinoma development after combined administration of lisinopril and tamsulosin: links to photocarcinogenesis and nitrosogenesis in the context of pharmaco-oncogenesis. Medical Review (Med. pregled), 2024 ;60(4): 67-72.

The authors declare no conflicts of interest.

Ethics approval statement is not required.

Written informed consent for publication of their details was obtained from the patient.

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