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CASE REPORT

ADVANCED SQUAMOUS CELL CARCINOMA OF THE SKIN INDUCED BY LONG-TERM HYDROXYUREA TREATMENT IN A PATIENT WITH ESSENTIAL THROMBOCYTHEMIA

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Abstract. Background and Objective: *SCCs represents 20-30% of the non-melanocytic skin cancers. It is the second most common skin cancer in the U.S. The main risk factors for SCCs development are: skin phototype I-II, excessive UV-exposure, chronic inflammatory skin diseases, radiation exposure and drug usage. Hydroxyurea is a drug used for the treatment of chronic myeloid leukemia, polycythemia vera and essential thrombocythemia. The therapy is associated with development of actinic keratoses, Bowen's disease, squamous cell carcinoma and basal cell carcinoma.* ***Patients and methods:*** *We present a 70-year-old female patient suffering from essential thrombocythemia, undergoing treatment with hydroxyurea since 2005, who developed advanced squamous cell carcinoma of the skin of the face and wrists.* ***Results:*** *The patient was diagnosed with advanced moderately differentiated SCCs (Grade 2), stage III (T4 N0 M0). Immunotherapy with cemiplimab 350 mg i.v. every 21 days was initiated. After 6 therapeutic cycles decrease of erythema and desquamation was registered. In 2022 the patient had an ischemic stroke, decompensated heart failure and acute kidney insufficiency. Unfortunately the patient died.* ***Conclusions:*** *Patients undergoing long-term hydroxyurea treatment are prone to develop multiple squamous cell carcinomas of the skin and are subject to regular dermatological examinations.*

Key words: *squamous cell carcinoma of the skin, essential thrombocythemia, hydroxyurea, cemiplimab*

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INTRODUCTION

We present a case of a 70-year-old female patient suffering from essential thrombocythemia (ET), undergoing treatment with hydroxyurea (HU) 1000 mg per day and low-dose aspirin since 2005, who developed advanced squamous cell carcinoma of the skin (SCCs) of the face and wrists.

In April 2022 the patient presented with an erythematous, scaly and painful skin eruption affecting the face and both of the wrists. She reported the rash had started in 2020 and aggravated after sun exposure. In 2021 extensive wounds on the skin of the wrists had appeared. In 2018 the patient had undergone surgical treatment of a SCCs on the back of the left wrist.

The pathological skin changes affected the skin of the face, both forearms and the dorsal surface of the wrists. They were presented by an erythematous maculopapular exanthema with slight desquamation. In the medial metacarpal area of the left wrist a tumor formation with diameter 4 cm, infiltrated edges raised above the surrounding skin and central ulceration covered with brownish crusts, was found (Fig. 1 a, b, c). Mucous membranes and skin appendages were not pathologically affected and peripheral lymph nodes were not enlarged. The patient reported tension and itching in the affected area. As differential diagnosis lupus erythemathosus, porphyria cutanea tarda and SCCs were discussed. The results from the complete blood count and biochemistry revealed high platelet (506 x 10^9/L) and uric acid level (8,92 mmol/L). Microbiological examination from left wrist wounds found Escherichia coli. The immunological results were in referent ranges. Examination of urine for porphyrins, under Wood light, was negative. Partial excisional biopsies of face and wrist tumor were performed. Histopathological examination revealed moderately differentiated SCCs in both areas (Fig. 2 a, b).

Based on the medical history, dermatological status, histopathological and the above mentioned laboratory investigations, the patient was diagnosed with advanced moderately differentiated SCCs (Grade 2), stage III (T4 N0 M0).

Therapy with ceftriaxon, gentamycin and chloropyramine hydrochloride was administered. The hematology consultation reduced the HU dosage to 500 mg per day and the patient was referred to the oncological committee.

In June 2022 treatment with cemiplimab 350 mg i.v. every 21 days was initiated.

In September 2022 a total body CT was performed and found no signs of progression of the SCCs and hepatosplenomegaly. After 6 therapeutic cycles we registered decrease of erythema and desquamation of the lesions on the face, both forearms and wrists. The infiltrative tumor formation in the left medial metacarpal area persisted and new nodular lesions on the dorsal surface of both wrists were found (Fig. 3 a, b). In November 2022 the patient had an ischemic stroke, decompensated heart failure and acute kidney insufficiency. The platelet level was 1325 x 10^9/L. The patient was hospitalised in the Hematology Clinic, where HU therapy was stopped and cytoreductive therapy with cytarabine was initiated. Unfortunately the patient died.

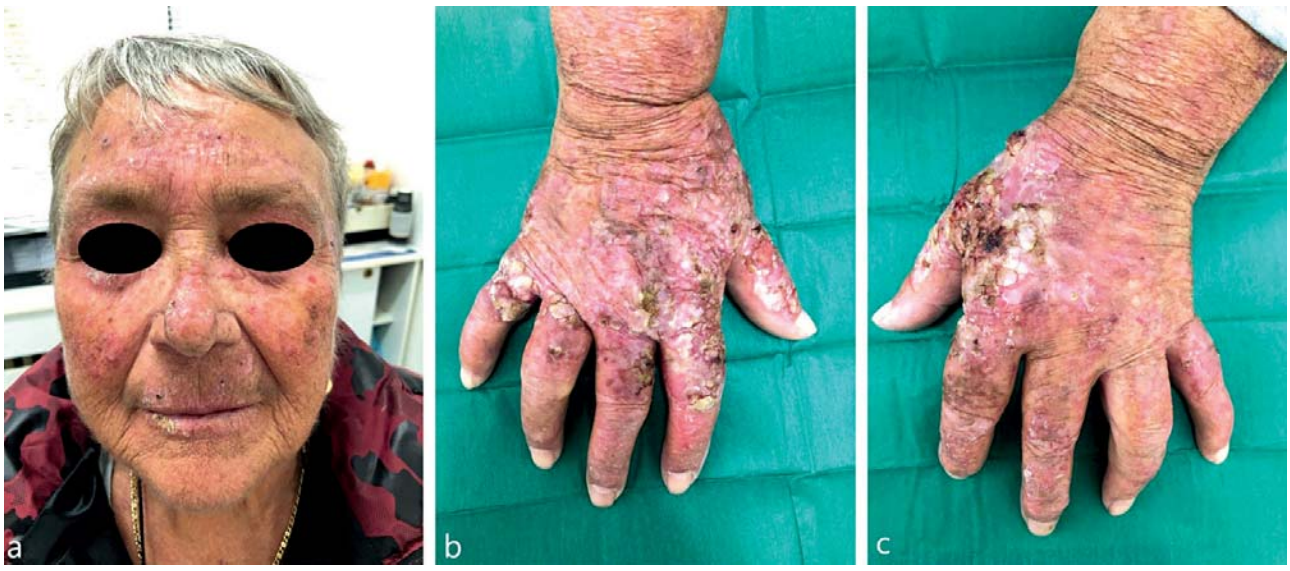

Fig. 1. a) Erythematous maculopapular exanthema with slight desquamation of the face **b, c)** Erythematous maculopapular rash of both wrists. A tumor formation with diameter 4 cm, infiltrated edges raised above the surrounding skin and central ulceration covered with brownish crusts in the medial metacarpal area

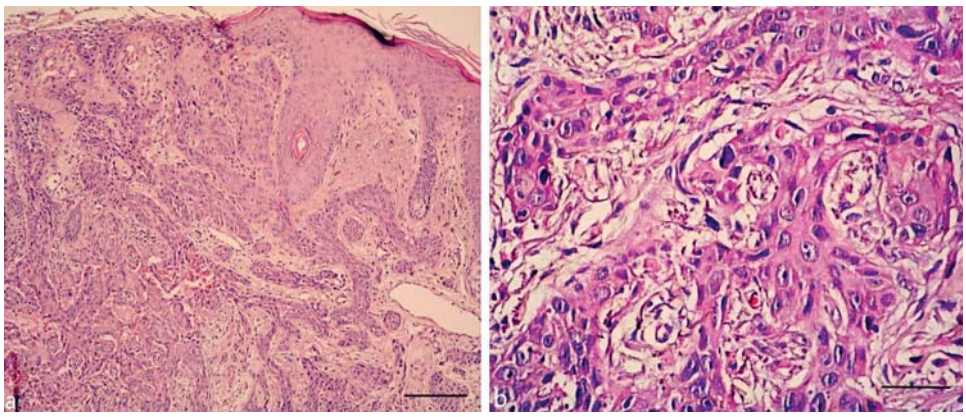

Fig. 2. a) Moderately differentiated SCCs of the left temporal area (hematoxylin-eosin stain, scale bar 200 μm) **b)** SCCs of the medial metacarpal area of the left wrist (hematoxylin-eosin stain, scale bar 50 μm)

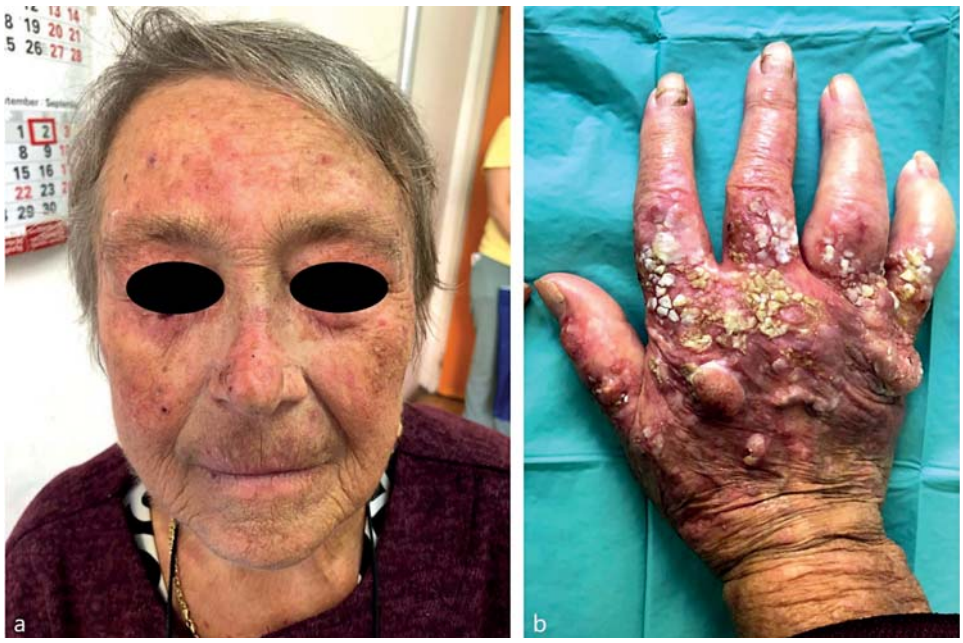

Fig. 3. a) Decreased erythema and desquamation of the facial lesions **b)** The tumor formation persisted and new nodular lesions on the dorsal surface of both wrists appeared

DISCUSSION

SCCs represents 20-30% of the non-melanocytic skin cancers. It is the second most common skin cancer with more than 1 million cases per year in the U.S. [1, 2]. Risk factors for SCCs development are skin phototype I-II, excessive UV-exposure, chronic inflammatory skin diseases, radiation exposure and drug usage, like in our case [3, 4]. Hydroxyurea is a metabolic inhibitor of ribonucleotide reductase and an alkylating myelosuppressive agent. It is used for treatment of chronic myeloid leukemia, polycythemia vera and ET. The most commonly described skin side effects of long-term HU treatment are facial erythema, hyperpigmentation, desquamation, hyperkeratosis, alopecia, acral erythema, palmoplantar keratodermia, melanonychia. [5]. The association of invasive SCCs in sun-exposed areas after HU treatment was first described in 1991 [6]. The therapy is also associated with development of actinic keratoses, Bowen's disease and basal cell carcinoma [7]. The skin toxicity from HU is persistant, despite withdrawal in most of the cases [8]. Sanchez-Palacios et al. described an UV-induced disease which they called "hydroxyurea-associated squamous dysplasia" which in theory precedes the development of SCCs [9]. In addition, HU can lead to elevation of p53 levels in the keratinocytes, which increases the risk of skin cancer development. HU also reduces DNA synthesis and DNA repair in ultraviolet-irradiated cells, changing the cell replication cycles in the epidermis [10-13]. This pathogenic mechanism explains the potential appearance of the SCCs on sun exposed skin, like in the case described herein.

In conclusion, patients undergoing long-term HU treatment are prone to develop multiple squamous cell carcinomas of the skin and are subject to regular dermatological examinations. We presented a rare case of advanced SCCs due to long-term HU treatment of ET in a 70-year-old female patient. Acute aggravation of the hematological condition unfortunately lead to the patient's death.

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REFERENCES

1. Corchado-Cobos R, García-Sancha N, González-Sarmiento R et al. Cutaneous Squamous Cell Carcinoma: From Biology to Therapy. Int J Mol Sci 2020; 21(8):2956.
2. Dourmishev A, Popova L, Dourmishev L. Basal and squamous cell carcinoma: sex, age and location distribution. Skin Cancer and UV Radiation. Berlin, Heidelberg: Springer Berlin Heidelberg, 1997. 540-546.
3. Waldman A, Schmults C. Cutaneous Squamous Cell Carcinoma. Hematol Oncol Clin North Am 2019; 33(1):1-12.
4. Tchernev G, Philipov S, Chokoeva A et al. A Patient with Multiple Keratinocyte Cancers (MKC): Uncommon Presentation in a Bulgarian Patient. Open Access Maced J Med Sci. 2018 Jan 25; 6 (1): 120-122.
5. Musiałek MW, Rybaczek D. Hydroxyurea-The Good, the Bad and the Ugly. Genes (Basel) 2021; 12(7):1096.
6. Disdier P, Harle JR, Grob JJ et al. Rapid development of multiple squamous-cell carcinomas during chronic granulocytic leukemia. Dermatologica 199; 183: 47-48.
7. Cantisani C, Kiss N, Naqeshbandi AF et al. Nonmelanoma skin cancer associated with Hydroxyurea treatment: Overview of the literature and our own experience. Dermatol Ther 2019; 32(5):e13043.
8. Xu Y, Liu J. Hydroxyurea-induced cutaneous squamous cell carcinoma: A case report. World J Clin Cases 2019; 7: 4091-4097.
9. Sanchez-Palacios C, Guitart J. Hydroxyurea-associated squamous dysplasia. J Am Acad Dermatol 2004; 51(2):293-300.
10. Broshtilova V, Gantcheva M. Urticarial Dermatitis–a Define Clinical Entity or a Predilection Histological Marker?. ANTHROPOLOGY AND ANATOMY 28 (2) 28: 38.
11. Sakano K, Oikawa S, Hasegawa K et al. Hydroxyurea induces site-specific DNA damage via formation of hydrogen peroxide and nitric oxide. Jpn J Cancer Res. 2001 Nov; 92(11):1166-1174.
12. Kerdoud O, Aloua R, Kaouani A et al. Squamous cell carcinoma during long term hydroxyurea treatment: A case report. Int J Surg Case Rep 2021; 85:106160.
13. Hoff NP, Akanay-Diesel S, Pippirs U et al. Kutane Nebenwirkungen einer Hydroxyurea-Therapie bei Polycythaemia vera. Hautarzt 60 2009: 783-787.