

Single Case

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# Squamous Cell Carcinoma as a Complication of Long-Term Hydroxyurea Treatment

Miłosz Lewandowski<sup>a</sup> Paweł Łukowicz<sup>b</sup> Jerzy Jankau<sup>c</sup>  
Jan Romantowski<sup>b</sup> Wioletta Barańska-Rybak<sup>a</sup>

<sup>a</sup>Department of Dermatology, Venereology and Allergology, Medical University of Gdansk, Gdansk, Poland; <sup>b</sup>Department of Allergology, Medical University of Gdansk, Gdansk, Poland; <sup>c</sup>Department of Plastic Surgery, Medical University of Gdansk, Gdansk, Poland

## Keywords

Squamous cell carcinoma · Hydroxyurea · Nonmelanoma skin cancer · Chemoprevention · Complication

## Abstract

Hydroxyurea therapy is commonly used in the treatment of patients suffering from myeloproliferative diseases, such as polycythemia vera. It is supported by evidence that this type of therapy can generate mild skin lesions like leg ulcers, erythema, and hyperpigmentation. There are also some studies that show an increased risk of development of nonmelanoma skin cancers. We report a 56-year-old man with a 13-year history of polycythemia vera, treated chronically with hydroxyurea. In April 2020, the patient presented a skin lesion on the forehead, skin horn on the left forearm, and hyperkeratosis on the rims of both ears. In the patient's history, in October 2019, complete excision of the skin lesion in the central area of the forehead was performed. After 4 months, a new skin lesion appeared at the same area of the forehead, which in May 2020 after resection in the histopathological examination was diagnosed as recurrence of squamous cell carcinoma. The aim of the case is to draw the clinicians' attention to the increased risk of squamous cell carcinoma and basal cell carcinoma in patients treated with hydroxyurea. Increased vigilance would make it possible to recognize them earlier, and thus potentially reduce the undesirable effects associated with the delayed radical treatment of these skin cancers. Randomized clinical trials assessing the potential benefits of oral retinoids for chemoprevention of nonmelanoma skin cancers in the hydroxyurea-treated population should also be considered.

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Published by S. Karger AG, Basel

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Correspondence to:  
Miłosz Lewandowski, [milosz.lewandowski@gumed.edu.pl](mailto:milosz.lewandowski@gumed.edu.pl)

## Introduction

Nonmelanoma skin cancer (NMSC), excluding basal cell carcinoma, was in 2018 the 5th most commonly new reported cancer worldwide [1]. The main risk factors of NMSC are excessive ultraviolet light exposure, chronic inflammatory skin conditions, exposure to radiation, and contact with arsenic [2]. An increased risk of developing NMSC is also observed during therapy with certain drugs, including hydroxyurea (HU), also known as hydroxycarbamide, though these drugs usually generate mild skin lesions, such as leg ulcers, erythema, and hyperpigmentation [2, 3].

We present a case report of a patient developing various skin lesions including SCC during 13 years of HU therapy during polycythemia vera treatment. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

## Case Description

A 56-year-old male patient has been suffering from polycythemia vera for 13 years. From the beginning of the disease, he was under constant care of a hematologist. As a treatment, he has taken HU, at a daily dose of 1,500–2,000 mg. Occasionally, following the hematologist's recommendations, the daily dose was increased to 3,000 mg. For 4–5 years, the patient has taken allopurinol 300 mg every 2 days due to elevated uric acid levels. On June 30, 2018, the patient underwent subtotal thyroidectomy, after which he suffered from iatrogenic hypothyroidism. He took levothyroxine 150 µg/day, additionally experiencing dry and peeling skin. He has also suffered from depression for several years although never took the prescribed medications. The family history of cancer was negative. The patient denied excessive exposure to the sun's rays and also solarium during his life. He worked as a car mechanic and denied exposure to chemicals or vapors during work. He also smoked cigarettes (1 pack a day for 20 years).

In August 2019, a small, red lesion appeared centrally on the forehead. After a dermatological consultation, SCC was suspected, and the patient was referred for excision of the lesion. The procedure took place in October 2019, and a change in the size of 14 mm × 10 mm was excised. Histopathological examination revealed the presence of G2 ulcerated SCC, complete removal with margins of 0.2 cm laterally and deeply. After the procedure, the patient claims that the wound had separated and tried to heal.

In the autumn of 2019, skin lesions appeared on the rims of both ears, which according to the patient were defined as precancerous conditions – keratosis. At the beginning of 2020, a slowly growing skin horn appeared on the left forearm, shown in Figure 1. In February 2020, a thickening appeared in the forehead wound, which began to purge and hurt and slowly turned into a tumor, shown in Figure 2.

The patient was admitted to the Department of Plastic Surgery of Medical University of Gdansk in May 2020 in order to excise a skin lesion measuring 50 mm × 50 mm located in the area of the forehead with suspicion of recurrence of SCC. Before the procedure, a CT scan of the head and neck was performed, which revealed probable infiltration of the frontal bone periosteum with cancer cells. No enlarged lymph nodes in the neck were detected. The next day, the lesion was excised with a 2-cm margin of macroscopically unchanged tissues, along with the chiseling of the bone to remove the periosteum. The histopathological examination revealed an exophytic tumor 43 mm × 37 mm × 12 mm, microscopically carcinoma planoepitheliale infiltrans, grade 2, with no neoplastic weaves in bone fragments. The patient was qualified for radiotherapy after the local condition had healed. Due to radiotherapy, a lapoplasty was ordered, during which another biopsy was performed at the site of the excised lesion, and the neoplastic tissue was not detected, shown in Figure 3.



**Fig. 1.** Skin horn appeared on the left forearm.



**Fig. 2.** Thickening in the forehead wound.



**Fig. 3.** Condition after plastic surgery.

## Discussion

Due to their activity profile, antineoplastic drugs can cause a number of skin lesions, including skin cancer (nonmelanoma) [4]. Rapidly growing cells are the target of chemotherapy, so chemotherapy often affects the skin, hair follicles, and nail matrix. Although there are relatively few studies describing patients with NMSC after hydroxycarbamide therapy in the literature, there have been more and more reports on this subject in recent years which underlined the significance of dermatologic follow-up [5, 6]. This stays in line with the conclusions of the 2019 review of the literature on NMSC with hydroxycarbamide treatment, which highlighted the role of the increased awareness of the possible dermatological toxicity of HU treatment [2]. Long-term follow-up of patients treated with HU is mandatory because recurrence of the NMSC tumor may occur several years after HU discontinuation. We did not observe any changes in the nails in our case; however, the literature describes cases of patients who developed melanonychia during HU therapy [7, 8]. There are no recommendations regarding the chemoprevention of NMSC in the population treated with HU [8]. However, some studies show that chemoprevention with oral retinoids can reduce the risk of development of SCC both in moderate-risk and high-risk patients [9, 10]. However, literature reviews underline the need for the creation of clear guidelines regulating the use of oral retinoids as chemoprevention of skin cancers [11, 12].

## Conclusions

All in all, case description together with current literature data highlights the possibility of NMSC as a side effect of HU therapy. It is worth considering conducting randomized clinical trials investigating potential benefits from oral retinoids supplied as chemoprevention of NMSC in a population treated with HU, especially for those who require prolonged therapy and develop any skin abnormalities. The aim of the case is also to draw the clinicians' attention to the increased risk of squamous cell carcinoma and basal cell carcinoma in patients treated with HU. Long-term follow-up of patients treated with HU might be recommended [8], and it would make it possible to recognize NMSC earlier, and thus potentially reduce the undesirable effects associated with the delayed radical treatment of these skin cancers.

## Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of the medical case and any accompanying images. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.

## Funding Sources

There were no funding sources.

### Author Contributions

Miłosz Lewandowski and Paweł Łukowicz conceived of the presented idea and collected the data from the patient. Miłosz Lewandowski, Paweł Łukowicz, and Jan Romantowski wrote the manuscript. Jerzy Jankau and Wioletta Barańska-Rybak assessed clinical usefulness of this case report and supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

### Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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