

Case Report

Merkel cell carcinoma associated with chronic treatment with hydroxyurea: a case report

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ABSTRACT

Merkel cell carcinoma is a rare neuroendocrine tumour of the skin, that shows a quickly and aggressive behaviour and carries a poor prognosis. Surgery is the standard primary treatment modality, while radiotherapy plays a role in postoperative treatment. Radiotherapy is also an alternative to unresectable lesions or patients who are unfit to surgery. Here we report a 90-year-old male with polycythemia vera that was chronically treated with hydroxyurea for about 30 years. The patient presented a purple and exophytic frontal scalp lesion, which had recurred after primary wide excision. This recurrence had been considered inoperable and the patient was treated with external beam radiotherapy to the lesion and locoregional lymph nodes, showing a complete clinical response after 12 weeks. However, disease progressed rapidly, and the patient died from distant metastasis 4 months later. This report is the second described case in literature of Merkel cell carcinoma as complication of chronic hydroxyurea and highlights the need for these patients to undergo regular and close dermatological evaluation.

Keywords: Merkel cell carcinoma, Hydroxyurea, Non-melanoma skin cancer, Radiotherapy, Immunosuppression, Risk factor

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare cutaneous neuroendocrine malignancy, with a global estimate incidence of 0.1-1.6 cases per 100.000 people per year.¹ It exhibits highly aggressive clinical features, frequent locoregional recurrence, and death from distant metastasis (DM).² The median time from initial diagnosis to recurrence is about 9 months.³

Characteristically, it presents as a painless, rapidly enlarging red or purple nodule, most often in sun-exposed areas on a person with fair skin.²

From the most differentiated to the least, and best prognosis to the worst, there are three histological types - trabecular, intermediate, and small cell - although the utility of these subtype classifications is not clear.⁴

The molecular mechanisms behind MCC remain in active research. Feng et al demonstrated a Merkel cell polyomavirus in about 80% of MCC samples.⁵ Additionally, other known risk factors include ultraviolet radiation, immunosuppression, and advanced age.^{1,2,6} The survival rate is markedly lower in immunosuppressed patients.⁷

The recommended primary initial treatment is surgery.⁶ However, in the head and neck (H&N), it is difficult to achieve wide local excision without major deformity and aesthetic commitment. For positive margins, large tumours, or positive lymph nodes (LN), postoperative radiotherapy (PORT) or chemoradiotherapy has superior survival over surgery alone.⁷ Primary radiotherapy (RT) can be considered in patients unfit for surgery, with equivalent locoregional control, but no effect on overall

survival (OS).⁶ Although it is a chemo- and radiosensitive disease, its responses are generally short-lived.

Here, it is described the second reported case, to our knowledge, of MCC as a complication of chronic hydroxyurea treatment.⁸

CASE REPORT

A 90-year-old Caucasian male was referred to our Department for RT to a MCC of the scalp. He had the diagnosis of polycythemia vera and was treated with hydroxyurea, 300-400 mg per os, once a day, for the last three decades, with multiple recurrent lesions of actinic keratosis in the face and scalp. A non-pigmented papule of about 9×10 mm in the frontal area had been surgically removed 4 months before our consultation, with histopathological examination of the excised specimen revealing dermal infiltration by MCC, with microscopic positive lateral margins. The clinical stage was I, according to the eighth edition of the American Joint Committee on Cancer staging. The lesion soon recurred, and the patient was referred to the Radiotherapy Department as he was considered unfit for extension of surgical margins.



Figure 1: Evolution of skin lesion during treatments – (A) before starting radiotherapy (RT), (B) after 28 Gy, (C) after 66 Gy, and (D) 3 months after completing RT.

Examination revealed various purple exophytic nodules located in the frontal area of the scalp (Figure 1A), measuring 110×60 mm. Neck, chest, abdomen, and pelvic computerized tomography scan were unremarkable, except for mild splenomegaly and hepatomegaly. No sentinel lymph node biopsy (SLNB)

was made, and there was no evidence of clinically positive nodes.

He was treated with external beam RT to the lesion (66 Gy) and locoregional LN (46 Gy), levels Ia, Ib, and IIa bilaterally, with 2 Gy/day, 5 days/week. During treatment, he presented radiodermatitis grade 2 in the frontal region and pharyngeal and oral radiomucositis grade 2, according to the Common Terminology Criteria for Adverse Events, version 4.03. There was a quick downsizing of the skin lesion throughout the course of the radiation treatment (Figure 1B and C) and a complete clinical response (Figure 1D) 12 weeks after conclusion of RT.

However, DM occurred quickly, and the patient died 4 months later.

DISCUSSION

Hydroxyurea is a cytostatic, non-competitive inhibitor of the ribonucleotide reductase.⁹ It is indicated as treatment of myeloproliferative disorders such as resistant chronic myelocytic leukemia, polycythemia vera, and essential thrombocythemia, as well as other diseases such sickle-cell disease and psoriasis.¹⁰ Although long-term use appears to be safe and tolerable, several clinically important adverse effects have been reported.¹¹

Among those, a higher incidence of non-melanoma skin cancer (NMSC), such as squamous and basal cell carcinoma, appears to be associated with chronic intake of hydroxyurea, sometimes after a prolonged latency period, and most often, in photo-exposed areas of the skin. This is explained by its potential for carcinogenesis by inhibiting repair of cutaneous deoxyribonucleic acid damage by ultraviolet.^{12,13} The association between hydroxyurea intake and MCC has been reported once in literature.⁸ This is the second case.

Hydroxyurea withdrawal results in improvement of the above described cutaneous lesions, which strengthens this association.¹² If there is clear indication for maintaining treatment with hydroxyurea, patients at high risk of developing invasive or metastatic NMSC, specially organ-transplant patients, may benefit from chemoprevention with low dose oral retinoids.¹⁴

After diagnosis and staging of a MCC, wide excision with SLNB is the standard management of the primary tumour, with or without PORT. However, in the H&N, a wide local excision may be difficult without damage of cosmesis and neurovasculature.¹⁵ SLNB positive or clinically node-positive patients should undergo completion dissection and/or RT, according to the National Comprehensive Cancer Network guidelines (NCCN), version 1.2020.

Indications for PORT include tumour >2 cm, close or positive surgical margins, lymphovascular space

invasion, LN positive, absence of LN evaluation, and immunocompromised patients.¹⁶ In addition, delays should be avoided as starting PORT after 6 weeks is associated with early recurrence (NCCN guidelines, version 1.2020).

A systematic review and meta-analysis showed a significant increase in OS with PORT (hazard ratio=0.81, $p<0.001$), but no effect in DM-free survival.¹⁶ The addition of concurrent chemotherapy to PORT brings no statistically significant difference to adjuvant treatment.¹⁷ For low-risk non-H&N tumour location, PORT may not be necessary.¹⁸ Primary RT can be considered in patients non-candidates for surgery, with locoregional in-field control rates of 75-85% and a reported 5-year OS rate of 40-60%.¹⁹

Song et al have recently described that, in MCC, the first site of the metastatic event is regional LN in 87%, including 73% with isolated LN involvement.²⁰ Twenty-eight percent of patients developed DM, showing some predilection for abdominal viscera (51%) and distant LNs (46%).

CONCLUSION

This is the second case reported in literature of MCC associated with chronic treatment with hydroxyurea. It emphasizes the necessity for regular and comprehensive dermatological examination for patients who undergo long-term hydroxyurea because skin lesions like MCC have a high morbidity and mortality. RT plays a role in locoregional control of the disease and appears to be well tolerated, even in elderly patients, with good aesthetic results.

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REFERENCES

- Schadendorf D, Lebbe C, zur Hausen A, Avril M, Hariharan S, Bharmal M, et al. Merkel cell carcinoma: Epidemiology, prognosis, therapy and unmet medical needs. *Eur J Cancer.* 2017;71:53-69.
- Koljonen V. Merkel cell carcinoma. *World J Surg Oncol.* 2006;4:1-11.
- Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. Merkel cell carcinoma: Prognosis and treatment of patients from a single institution. *J Clin Oncol.* 2005;23:2300-9.
- Jaeger T, Ring J, Andres C. Histological, Immunohistological, and Clinical Features of Merkel Cell Carcinoma in Correlation to Merkel Cell Polyomavirus Status. *J Skin Cancer.* 2012;2012:1-5.
- Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science.* 2008;319:1096-100.
- Lebbe C, Becker JC, Grob JJ, Malvehy J, Marmol V, Pehamberger H, et al. Diagnosis and treatment of Merkel Cell Carcinoma. European consensus-based interdisciplinary guideline. *Eur J Cancer.* 2015;51:2396-403.
- Paulson KG, Iyer JG, Blom A, Warton EM, Sokil M, Yelistratova L, et al. Systemic immune suppression predicts diminished merkel cell carcinoma-specific survival independent of stage. *J Invest Dermatol.* 2013;133:642-6.
- Bouldouyre M-A, Avril M-F, Gaulier A, Sigal-Grinberg M. Association of cutaneous side-effects of hydroxyurea and neuroendocrine carcinoma. *Eur J Dermatol.* 2005;15:268-70.
- Singh A, Xu YJ. The cell killing mechanisms of hydroxyurea. *Genes (Basel).* 2016;7.
- Madaan K, Kaushik D, VerM.A. T. Hydroxyurea: A key player in cancer chemotherapy. *Expert Rev Anticancer Ther.* 2012;12:19-29.
- Steinberg MH, McCarthy WF, Castro O, Ballas SK, Armstrong D, Smith W, et al. The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: A 17.5 year follow-up. *Am J Hematol.* 2010;85:403-8.
- Cantisani C, Kiss N, Naqeshbandi AF, Tosti G, Tofani S, Cartoni C, et al. Nonmelanoma skin cancer associated with Hydroxyurea treatment: Overview of the literature and our own experience. *Dermatol Ther.* 2019;32:1-7.
- Disdier P, Harle JR, Grob JJ, Weiller-Merli C, Magalon G, Waller PJ. Rapid development of multiple squamous-cell carcinomas during chronic granulocytic leukemia. *Dermatology.* 1991;183:47-8.
- Soltani-Arabshahi R, Tristani-Firouzi P. Chemoprevention of nonmelanoma skin cancer. *Facial Plast Surg.* 2013;29:373-83.
- Raju S, Vazirnia A, Totri C, Hata TR. Treatment of Merkel cell carcinoma of the head and neck: A systematic review. *Dermatologic Surg.* 2014;40:1273-83.
- Petrelli F, Ghidini A, Torchio M, Prinzi N, Trevisan F, Dallera P, et al. Adjuvant radiotherapy for Merkel cell carcinoma: A systematic review and meta-analysis. *Radiother Oncol.* 2019;134:211-9.
- Hasan S, Liu L, Triplet J, Li Z, Mansur D. The role of postoperative radiation and chemoradiation in Merkel cell carcinoma: A systematic review of the literature. *Front Oncol.* 2013;3:1-10.
- Goff PH, Bierma M, Lachance K, Schaub SK, Tseng YD, Liao JJ, et al. Primary Tumor Location As a Potential Risk Factor for Local Recurrence in Resected, Low-risk Merkel Cell Carcinoma: Implications for Postoperative Radiotherapy. *Int J Radiat Oncol.* 2020;108:S132.
- Gunaratne DA, Howle JR, Veness MJ. Definitive radiotherapy for Merkel cell carcinoma confers clinically meaningful in-field locoregional control: A review and analysis of the literature. *J Am Acad Dermatol.* 2017;77:142-8.

20. Song Y, Azari FS, Tang R, Shannon AB, Miura JT, Fraker DL, et al. Patterns of Metastasis in Merkel Cell Carcinoma. *Ann Surg Oncol*. 2021;28:519-29.

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