

# Treatment of locally advanced cutaneous Merkel cell carcinoma with topical imiquimod



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## INTRODUCTION

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine tumor of the skin. Risk factors for MCC include advanced age (>65 years), fair skin, immunosuppression, sun exposure, and infection with Merkel cell polyomavirus.<sup>1,2</sup>

Evidence suggesting that the immune system plays a role in the host response to MCC<sup>3</sup> has directed therapeutic focus toward immunotherapy in treating advanced disease. Imiquimod is an immunomodulatory agent, it generates potent antiviral and anti-tumor activity through modification of innate and adaptive immune responses.<sup>4</sup> It has a well-established role in treating superficial basal cell cancer, squamous cell cancer in situ, and premalignant actinic field change and theoretically should target other cutaneous malignancies including MCC.<sup>5</sup>

We present a case of locally advanced and regionally metastasized MCC in a patient with a complex clinical scenario, where first-line therapies could not be used. This led us to trial the off-label use of 5% topical imiquimod cream as palliative treatment.

## CASE REPORT

A 77-year-old man was diagnosed with MCC of the right side of the forehead staged as T1N0M0. Following wide local excision, adjuvant radiotherapy was delivered to the primary site and draining nodal basins. During radiotherapy, his renal function deteriorated significantly (estimated glomerular filtration rate declined from 38 to 6 mL/min), requiring short-term dialysis. The acute drop was attributed to tissue lysis and inflammation in the setting of pre-existing IgA nephropathy, and radiotherapy was ceased. Chemotherapy and systemic

### Abbreviation used:

MCC: Merkel cell carcinoma

immunotherapy were contraindicated due to critically poor renal function and the potential for added nephrotoxicity.

Unfortunately, he developed rapid cutaneous recurrence at 6 months, with a large, deeply ulcerated lesion measuring 5 cm × 6 cm and multiple small satellite nodular cutaneous metastases on the scalp and upper portion of the forehead (Fig 1, A). Biopsy of the ulcerated lesion and 2 satellite lesions confirmed MCC. Given the number and wide distribution of these cutaneous metastases, he was no longer a surgical candidate and was referred for consideration of local therapeutic options.

At presentation, no lymphadenopathy was detected on examination and positron emission tomography scans did not reveal distant metastatic disease. Following consent for off-label use, he was commenced on a regimen of 5% topical imiquimod cream, applied once daily for 5 days each week. Treatment included the larger lesion (including the ulcerated surface) and all visible nodular satellite metastases. The cream was applied using a gloved finger and left on for at least 8 hours. The treatment was continued for a total of 35 weeks. He did not develop any significant local or systemic adverse reactions necessitating treatment modification. His renal function and baseline blood tests remained stable.

Nodular cutaneous metastases demonstrated an appreciable reaction within 2 weeks (Fig 1, B) and melted away after 8 weeks of treatment. The large, ulcerated lesion showed gradual and complete

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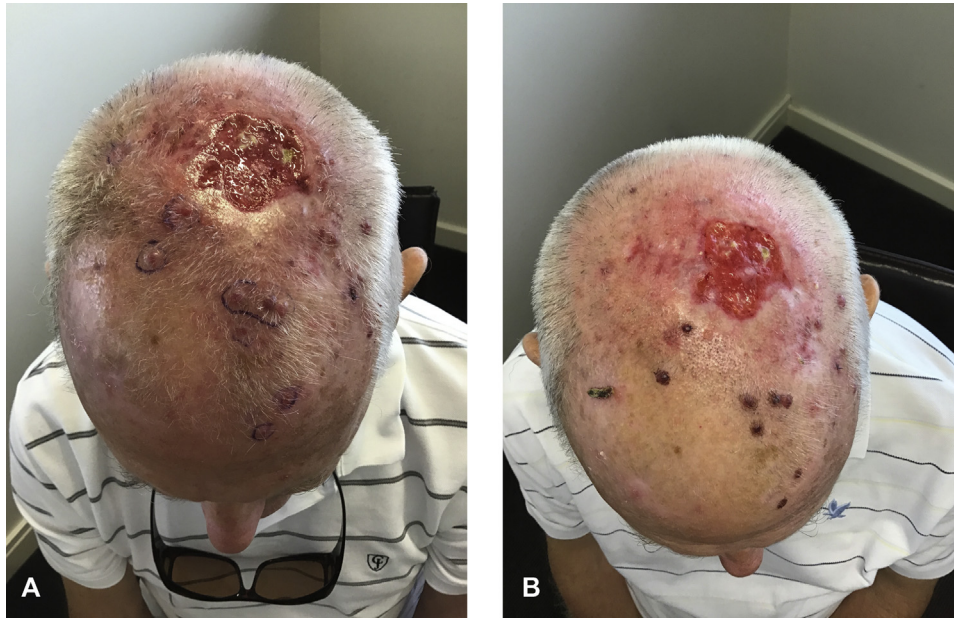
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**Fig 1.** **A**, Cutaneous metastases and ulcerated lesion at the initial visit. **B**, Cutaneous metastases at 2 weeks after commencing imiquimod showing an inflammatory reaction.

healing over 38 weeks (Fig 2, A and B) with sparse hair regrowth.

Following 35 weeks of imiquimod treatment, a total of 9 biopsies had been taken from the central lesion (at weeks 0, 8, 14, and 20 after treatment). The biopsy at week 0 was taken while the area was still granulating and ulcerated, with further biopsies taken after clinical healing. No evidence of MCC on hematoxylin-eosin or immunohistochemical staining was found in any of the biopsies. Instead, these showed lymphocytic inflammation, which progressively diminished in inverse proportion to scar tissue formation with time. Tissue T-cell gene rearrangement studies demonstrated a polyclonal T-cell population, consistent with what has been observed in earlier studies with the use of imiquimod.<sup>6</sup> Post treatment positron emission tomography scanning week 20 after treatment and clinical reviews between week 28 and week 70 did not reveal distant metastatic disease or evidence of local recurrence or lymphadenopathy.

## DISCUSSION

MCC has a high rate of progression to lymph node and distant organ metastasis. The first-line treatment for MCC is surgical excision of local disease followed by adjuvant radiotherapy.<sup>7</sup> While various chemotherapy regimens have been used for metastatic disease, there is no evidence-based protocol demonstrating improved overall survival.<sup>8</sup>

Clinical immunotherapy trials of programmed cell death protein 1/programmed death-ligand 1 inhibitors as first-line therapy have shown durable responses in approximately 50% of patients with advanced MCC.<sup>9,10</sup> Both avelumab and pembrolizumab are recommended by the United States Food and Drug Administration for treatment of patients with recurrent, locally advanced, or metastatic MCC.<sup>10</sup>

Our case highlights a common problem: patients with MCC are often older and may have significant comorbidities that limit or contraindicate the use of standard therapeutic interventions. Reported nephrotoxicity precluded the use of systemic immunotherapy in our patient,<sup>11</sup> leading us to trial 5% topical imiquimod as a palliative approach.

Full histologic and clinical resolution was observed after 35 weeks of treatment, with sustained remission after 70 weeks. T-cell gene rearrangement studies did not demonstrate clonal T-cell expansion, which has been reported in cases of spontaneous regression of MCC.<sup>12</sup> Of note, all follow-up biopsies showed a brisk mixed polyclonal lymphocytic infiltration, suggesting therapy-driven local immune-mediated tumor destruction, highlighting the role of immunomodulation in treating this malignancy.

In this case, monotherapy with topical imiquimod for locally advanced MCC was effective and tolerated well and should be considered in circumstances where standard therapy is contraindicated.



**Fig 2.** **A**, At week 18 of imiquimod treatment. **B**, 28 weeks after completed treatment.

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#### Conflicts of interest

None disclosed.

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