Merkel cell carcinoma can be indolent: A case with 7 locoregional recurrences over 15 years highlights the importance of patient-tailored management

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INTRODUCTION

Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine cutaneous malignancy.[1] Patients who develop recurrences or metastases usually have poor prognoses and are often treated aggressively.[1] We report a case of a man with an indolent, unusually long course of MCC over 15 years with 7 locoregional recurrences before developing distant metastases. Because he had 4 major comorbidities at baseline, less aggressive therapies were chosen for his recurrences, and there was no evidence of disease for the vast majority of his 15-year course.

Abbreviation used:

MCC: Merkel cell carcinoma

CASE REPORT

In 2005, a 71-year-old man with active stage IB cutaneous T-cell lymphoma (previously treated with numerous topical and systemic modalities), stage 3 chronic kidney disease, coronary artery disease, and ulcerative colitis presented with a painless, 3.5-mm erythematous papule of the left naris. Biopsy demonstrated MCC. He was treated with wide local excision and radiotherapy to the primary site. Sentinel lymph node biopsy was not performed. Platinum/etoposide chemotherapy was administered to treat a kidney lesion, initially thought to be metastatic MCC, which was later found to be renal cell carcinoma and treated with radiofrequency ablation.

He did well for 4 years until 2009, when he presented with a 2-mm recurrent MCC of the right earlobe (Fig 1). Restaging positron emission tomography-computed tomography showed no evidence of distant disease. The prolonged time to locoregional recurrence and the small size of the recurrent lesion suggested his MCC might be less aggressive than typical cases. Additionally, given his comorbidities and general frailty, general anesthesia and wide excision were avoided, and he was treated with Mohs micrographic surgery only. Of note, a DNA sequence comparison between the primary lesion and this recurrent lesion revealed an identical Merkel cell polyomavirus truncation mutation, indicating that subsequent MCCs likely arose from the original tumor in 2005 and did not represent independent primary lesions.

He remained disease-free for another 4 years until 2013, when he was diagnosed with his second

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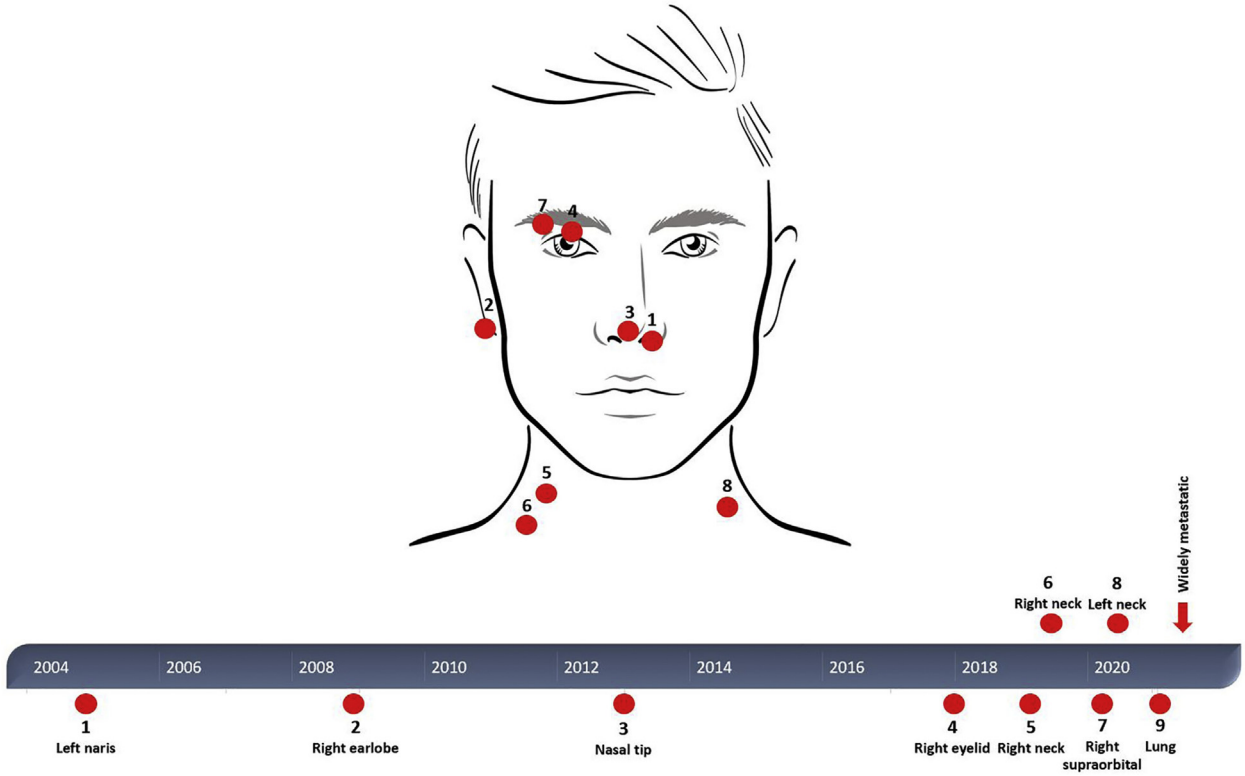

Fig 1. Merkel cell carcinoma timeline. The time course and locations of the patient's primary Merkel cell carcinoma and recurrences. Background facial illustration courtesy of Iuliia Stephashova/Shutterstock.com.

recurrence, a small papule on the left nasal tip, which was treated with narrow excision. After being disease-free for another 5 years, in 2018, he presented with his third recurrence on the right upper eyelid (Fig 2, *A*), for which he underwent oculoplastic surgery with lid reconstruction.

In March 2019, a fourth locoregional recurrence presented as a 2-cm subcutaneous nodule involving the right side of the inferior aspect of the neck (Fig 2, *B*). He underwent debulking surgery under conscious sedation followed by single-dose hypofractionated radiotherapy of 8 Gy. Histology showed MCC involving the fibroadipose tissue (Fig 3).

After 2019, his disease course accelerated, while his renal function deteriorated to stage 4 chronic kidney disease. In September 2019, he developed a fifth recurrence, a 1.5-cm subcutaneous nodule on the right side of the neck, for which he received radiotherapy of 25 Gy in 5 fractions. In February 2020, a right supraorbital nodule was diagnosed as his sixth recurrence. A positron emission tomography-computed tomography scan showed no disease outside this nodule. Gamma knife radiosurgery with a total of 18 Gy was completed with resolution of the lesion. In March 2020, a biopsy of a left side of the anterolateral aspect of the neck nodule showed a seventh locoregional recurrence

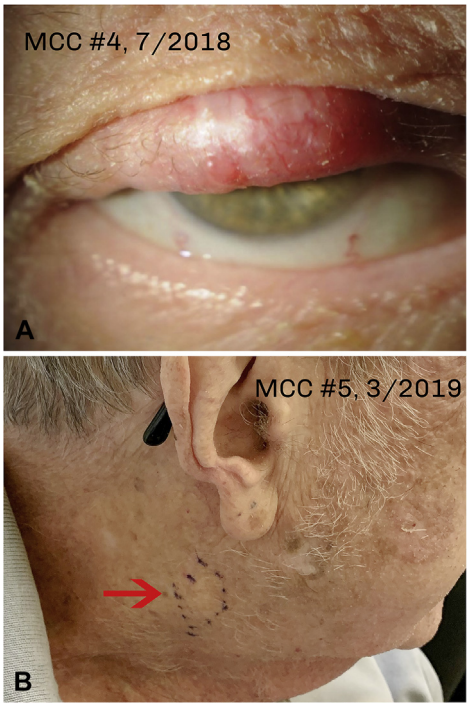

Fig 2. Merkel cell carcinoma recurrences. **A**, The fourth Merkel cell carcinoma, an erythematous mass on the right upper eyelid, managed with oculoplastic surgery with lid reconstruction. **B**, The fifth Merkel cell carcinoma, a 2-cm subcutaneous nodule (*red arrow*), managed with debulking surgery and single-dose hypofractionated radiotherapy of 8 Gy. *MCC*, Merkel cell carcinoma.

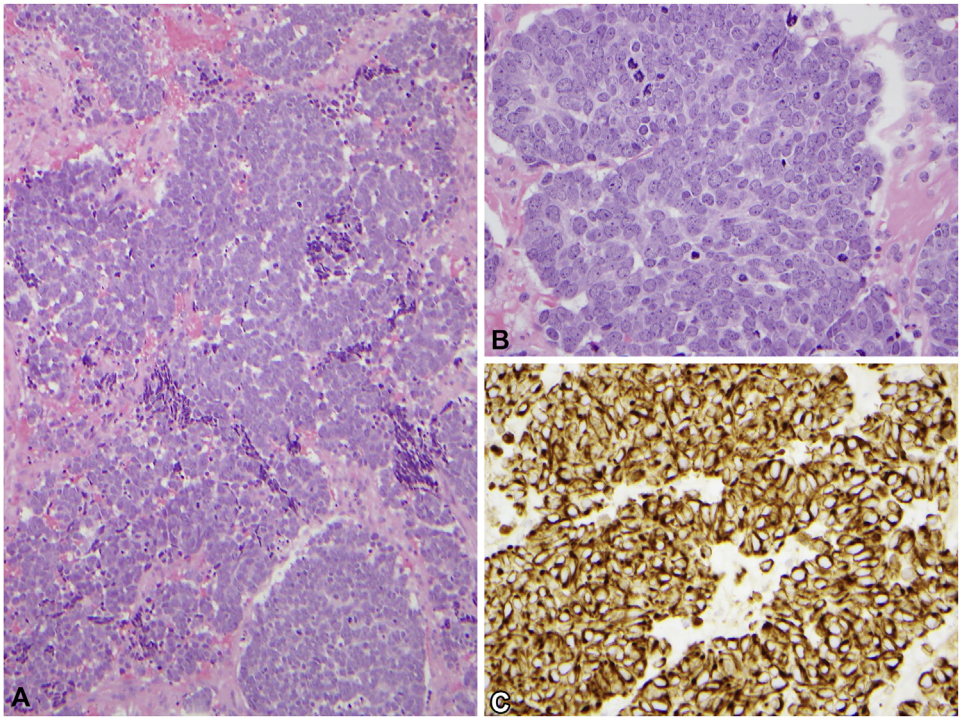

Fig 3. Histopathology of the fifth Merkel cell carcinoma. **A**, Very dense sheets of blue cells. **B**, Crowded blue cells with prominent nucleoli, vesicular nuclei, and scattered mitotic figures. Focal nuclear molding is also present. **C**, Diffusely positive CK20 staining in a perinuclear dot pattern. (**A** and **B**, Hematoxylin-eosin stain; **C**, CK20 stain; original magnifications: **A**, ×20; **B**, ×40; **C**, ×40.)

which was treated with excision and a short course of radiotherapy.

In April 2020, he developed a biopsy-confirmed right lung lesion, representing his first distant metastatic MCC. Since he was too frail to undergo excision or systemic therapies, he was treated with radiotherapy. In August 2020, the patient fell and fractured his left humerus, prompting a positron emission tomography-computed tomography scan that showed extensive bony metastases, involving all extremities, the ribs, vertebrae, and clavicle. He rapidly developed widespread cutaneous metastases, was treated with palliative radiation, and passed away 1 month later.

Overall, the patient had 7 biopsy-proven recurrences of MCC restricted to the head and neck over 15 years before developing distantly metastatic disease (Fig 1).

DISCUSSION

Although the present case is clearly an outlier, MCC is known to be an aggressive malignancy, and many patients are thus treated with extensive surgery, radiation, and systemic therapies.[1] Indeed, among all patients with MCC, the 5-year disease-specific survival has been reported to be approximately 64%, and patients with metastatic MCC have a particularly poor prognosis, with a 5-year overall survival of approximately 11% in the era before immunotherapy.[2] As such, the 15-year disease course of our patient with 7 locoregional recurrences is remarkably long. The protracted intervals between his recurrences are also unusual, as 80% of MCC recurrences arise within 2 years of diagnosis, and 96% present within 4 years.[3] Each of our patient's first 4 MCCs was separated by 4 years or more. To the best of our knowledge, indolent MCC has not been well described. With a long disease course and prolonged intervals between recurrences, this case highlights that MCC can occasionally behave in a less aggressive manner and illustrates the importance of patient-specific management.

The National Comprehensive Cancer Network lists sentinel lymph node biopsy, surgical excision, and/or radiotherapy as considerations for the management of early-stage MCC.[4] For advanced disease, systemic treatment is generally the mainstay of therapy. Immunotherapy has shown promising efficacy in recent trials and has replaced cytotoxic

chemotherapy as the frontline systemic therapy for advanced MCC in most cases due to its greater durability of response and improvement of overall survival.[5,6] Given the patient's general frailty and history of ulcerative colitis, our patient was not a good candidate for immunotherapy.

Although aggressive treatment is often chosen for patients with MCC, particularly for recurrences or metastases, treatments should be discussed by a multidisciplinary team and tailored to each patient's overall health and disease course.[7] Indeed, in some cases, less morbid treatments such as narrow-margin surgery and hypofractionated radiotherapy should be considered, especially in patients with extensive comorbidities.[7] Sparing our patient highly morbid treatments allowed him to maintain excellent quality of life for 15 years, during the vast majority of which he had no evidence of disease.

In conclusion, we report a patient with an unusually long disease course of MCC whose recurrences were treated conservatively. This case highlights the fact that MCC can behave indolently and that multidisciplinary, patient-specific care is essential in ensuring optimal outcomes.

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Conflicts of interest

Dr Nghiem reports grants from Bristol-Myers Squibb and EMD Serono and advisory fees from EMD-Serono, Pfizer, and Merck & Co. Author A. Breneman and Drs Akaike, Paulson, and D. Breneman have no conflicts of interest to declare.

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