Metastatic Merkel cell carcinoma and malignant melanoma in a single sentinel lymph node

Amanda Hamilton¹, Prasad Jayaratne² and Mark Zonta³

Abstract
Merkel cell carcinoma (MCC) and malignant melanoma are aggressive skin cancers that usually arise in sun-exposed parts of the body. This report describes an 85-year-old man who underwent a wide local excision and sentinel lymph node biopsy for primary MCC and was subsequently found to have metastatic MCC and malignant melanoma within the left inguinal sentinel lymph node. Dual diagnoses of aggressive cutaneous carcinomas, although rare, may become more common in regions of high ultraviolet exposure and an ageing population. Currently, there are no guidelines for treating synchronous MCC and melanoma, however, immunotherapy with PD-1 inhibitors and anti-CTLA-4 receptor antagonists have shown therapeutic effect against these two cancers and should be considered in treatment planning.

Keywords
Metastatic, melanoma, Merkel cell carcinoma, wide local excision, sentinel lymph node biopsy, neuroendocrine, BRAF, immunotherapy, radiation and chemotherapy

Introduction
Merkel cell carcinoma (MCC) and malignant melanoma are both aggressive cutaneous carcinomas. MCC is approximately 40 times rarer than melanoma but both are typified clinically as painless lesions of sun exposed areas with a propensity for nodal invasion and distant metastasis.¹

MCC is a neuroendocrine tumour initially named after Merkel cells due to their similar appearance; however, the progenitor cell remains unknown and is poorly understood.² Merkel cell polyomavirus (MCPyV) has been associated with up to 80% of cases of MCC found in the Northern Hemisphere and may be the causative agent in gene mutation and consequent malignant transformation of the cell when the immune system is suppressed.³–⁵ In the remaining cases where the virus is undetectable, including the majority of cases in Australia, high ultraviolet (UV) exposure is still the leading explanation as it induces a signalling pathway that stimulates expression of genes in fibroblasts responsible for development of MCC.⁶,⁷

While more common than MCC and accounting for approximately 75% of skin cancer-related deaths, melanoma is currently thought to be due to a transformed melanocytic stem cell that undergoes uncontrolled growth secondary to sporadic and/or familial mutations. Normally melanocytes are found in the epidermis, producing melanin to protect the cells by absorbing UV radiation. Non-cancerous growth of melanocytes results in freckles and moles, hence patients with large numbers of freckles and moles are at higher risk of melanoma. Although most common on sun exposed areas, with highest incidence in males being the back (35%), melanomas have been found on all parts of the body, including genitals, eyes, and gastrointestinal mucosa.

Given the high UV light exposure to the population in North Queensland, it is no surprise that the incidence of the two most aggressive skin cancers are higher than the national average. Further to this, with an ageing population present in

¹Townsville University Hospital, Townsville, QLD, Australia
²Sullivan Nicolaides Pathology, Mater Hospital Pimlico, Townsville, QLD, Australia
³North Queensland Minimally Invasive Surgery, Mater Hospital Pimlico, Townsville, QLD, Australia

Corresponding Author:
Amanda Hamilton, Townsville University Hospital, 100 Angus Smith Drive Douglas, Townsville, QLD 4810, Australia.
Email: amanda.hamilton2@health.qld.gov.au

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combination with immunosuppressed patients, multiple skin cancers in individuals is expected to rise.

**Case report**

This is a case of an 85-year-old Caucasian man who was referred to a general surgeon for further management of a MCC on his left leg after excision of the non-pigmented nodule was thought to be a basal cell carcinoma (BCC). Histopathology revealed a 20mm tumour staining positive for synaptophysin and CK20, extending into the subcutis with suspicion of lymphovascular invasion and involving the deep resection margin.

Clinical examination found no signs of locoregional or distant disease and no other new primary skin cancers. Positron emission tomography computed tomography (PET CT) scan was clear of metastatic disease and the risks and benefits of surgery including wide local excision (WLE) and sentinel lymph node biopsy (SLNB) were discussed with the patient.

The patient underwent a WLE of his MCC with a 2cm margin to deep fascia and a split skin graft was used to cover the defect. A left inguinal sentinel lymph node was removed based on preoperative lymphatic mapping and intra-operative patent blue dye. Histopathology showed residual MCC at the initial excision site and in the subcutaneous fat and dermal lymphatics. Surgical margins were clear but narrow. The sentinel lymph node was positive for multiple deposits of metastatic MCC; the largest measuring 3 mm, and a 6 mm deposit of metastatic malignant melanoma. BRAF testing of the melanoma was positive for V600K mutation. Please refer to Appendix 1, Images 1–5 for histopathology slides.

After multi-disciplinary review by the medical and radiation oncologists the patient declined any further treatment of his metastatic disease. At 6 months follow-up, there was no clinical evidence of recurrence and PET CT demonstrated no evidence of metastatic disease.

**Discussion**

This is a rare case of a SLNB with synchronous metastatic MCC and melanoma in a patient with no known history of melanoma. Consequently, a dual diagnosis of metastatic melanoma with unknown primary and metastatic MCC involving a left inguinal sentinel node has been made. This patient had many high-risk factors for both melanoma and MCC including a previous history of multiple skin cancers, increased age, high UV exposure as a North Queensland farmer and inherited phenotypic traits including fair skin type and male sex.8,9

Our patient underwent a WLE and SLNB for his MCC with clinically occult nodal disease according to current recommendations for the first line management of MCC. The SLNB was performed at the time of WLE to minimise disruption of the draining lymphatics to improve accuracy of the procedure since the incidence of nodal disease at initial presentation is up to 38% in patients with MCC.10–12 The WLE was successful in achieving complete excision of the MCC from the primary site, albeit with narrow margins, and the SLNB was positive for nodal spread with multiple deposits of MCC identified in the left inguinal sentinel node.

The incidental finding of metastatic melanoma in the sentinel inguinal node tested positive for BRAF V600K mutation. Regardless of patient history of primary melanoma, current guidelines for patients with BRAF mutation positive metastatic melanoma advise BRAF and MEK inhibitors and for long term surveillance of regional lymph node basins and for metastatic disease. Those patients with an occult primary should also undergo further assessment with a complete skin examination including the ears, eyes, scalp, upper and lower gastrointestinal tract and review of all pathology of previous skin excisions.13,14 Reassessment of our patient following the diagnosis of metastatic melanoma did not identify a primary tumour.

Patients presenting with metastatic melanoma and an occult primary melanoma is a recognised phenomenon and occurs in 10%–15% of cases. These patients have comparable or improved outcomes with recommended treatment, which may include a therapeutic nodal dissection, compared to those patients with a history of primary melanoma who undergo similar treatment.13,14

The status of the sentinel node is an important prognostic indicator in melanoma and MCC and assists in accurate treatment planning by assessing pathological disease staging.10,11,13,15,16 Final staging for our patient with metastatic MCC was stage IIIA with 5-year survival being 52% with recommended treatment.12 Staging of the melanoma based on an unknown primary and subclinical nodal disease is T0N1a with 5-year survival being 65% with recommended treatment.13 However, our patient declined further treatment for either cancer.

Current guidelines for MCC with a positive SLNB recommend a completion lymph node dissection and adjuvant radiation to the primary tumour bed and the regional lymph node basin to reduce the risk of locoregional recurrence and improve survival outcomes.12

Radiation for skin cancer on the leg of an elderly person raises concern of the potential risk of a non-healing wound from poor tissue perfusion and special care needs to be considered in this group of patients such as additional allied health support, wound care and regular reviews. Furthermore, the risk of lymphoedema is significant after lymphadenectomy and postoperative radiation, worsening a patient’s quality of life, particularly in this age group where there is already a general decline in health and increase in comorbidities. The risk versus benefit must be weighed up with functional reserve and patient’s life expectancy which is scored by Eastern Cooperative Oncology Group (ECOG) classification.17,18
Adjuvant chemotherapy for MCC has largely been abandoned due to lack of evidence to support an improved survival benefit, however if chemotherapy is being considered, then cisplatin with or without etoposide is currently recommended by the National Comprehensive Cancer Network. Occasionally, systemic treatment with carboplatin prior to radiation can be used to improve radiosensitivity of MCC. Novel evidence-based systemic treatment options have emerged using immunotherapy to target immune checkpoint pathways for MCC. Avelumab is a human monoclonal antibody that inhibits PD-L1 and is approved as a first line treatment in Australia and other countries for metastatic MCC. (Javelin Merkel 200 Trial). Other therapies currently being used include PD-1 inhibitors Pembrolizumab and Nivolumab, and Ipilimumab, an anti-cytotoxic T-lymphocyte-associated antigen (CTLA-4) antibody to potentiate antitumour response.

For patients with BRAF V600 mutation positive metastatic melanoma, current Australian guidelines recommend the combination of BRAF and MEK inhibitors (dabrafenib with trametinib or vemurafenib with cobimetinib) as targeted treatment to improve response to therapy, progression free survival and overall survival. Studies with the use of the immunotherapy agent nivolumab had shown a complete response rate of 16% response rate and is better tolerated and with less adverse events in the adjuvant treatment of unresectable stage III melanoma compared to ipilimumab alone which demonstrated a 5% response rate but when used in combination with ipilimumab had a complete response rate of 19%. The overall survival rate was 58% (median overall survival 3 years) when used in combination versus 44% for nivolumumab and 34% for ipilimumab alone and was found to have the greatest benefit in patients with either PD-L1 negative, BRAF mutation positive melanoma and elevated LDH levels.

Furthermore, there have been good responses to PD-1 inhibitors in the adjuvant treatment of MCC from the MCPyV positive group and a good response to PD-1 inhibitors with anti-CTLA-4 antibody in the MCPyV negative group; however, anti-CTLA-4 antibodies are known to cause more adverse systemic effects due to their toxicity. While studies are ongoing in this area, there are no available conclusive results for adjuvant treatment of MCC with immunotherapy.

For our patient population in Australia, it should be anticipated that dual diagnoses of MCC and malignant melanoma will increase given that we have the highest incidence of MCC and melanoma in the world, along with the greatest incidence of MCPyV negative MCC, and an ageing population of Australia. It is imperative that we are moving forward with adequate treatment planning for dual diagnoses of MCC and melanoma. To extrapolate treatment from current data available, it is suggested that BRAF/MEK inhibitors or immunotherapy could be recommended to treat patients with a dual diagnoses of metastatic MCC and metastatic melanoma, however, further studies are warranted.

Conclusion
In summary, we have described an 85-year-old gentleman who underwent a WLE and SLNB for primary MCC and was subsequently found to have metastatic MCC and malignant melanoma within a single left inguinal sentinel lymph node. Our patient declined further treatment, but he could have been considered for completion lymph node dissection with adjuvant radiation to the primary tumour bed and regional lymph node basin for the metastatic MCC. However, there is still ongoing debate regarding best management of metastatic MCC given the regular use of adjuvant radiation, which has no demonstrable survival benefit and the efficacy of immunotherapy in advanced MCC. Current recommendations for the BRAF V600K mutation positive melanoma are BRAF/MEK inhibitor and long-term surveillance of regional LN basins for metastatic disease. Again, lymphadenectomy has no survival benefit for malignant melanoma. Finally, there are no studies nor recommendations for treating synchronous MCC and melanoma, which is highly concerning given the global increase of the ageing population, immunosuppressed patients and high UV exposure. It is predicted that although rare, dual diagnoses of melanoma with MCC will become increasingly common. Subsequently, clinicians should be planning ahead for future therapies that will be appropriate and effective in treating melanoma with MCC.

Acknowledgements
We thank the patient and his family for allowing publication of this report. All authors listed above agree to publication of this case report.

Declaration of conflicting interests
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval
Our institution does not require ethical approval for reporting individual cases or case series.

Funding
The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent
Written informed consent was obtained from the patient for their anonymized information to be published in this article. This informed consent is maintained in the medical records for this patient.

Informed written consent was obtained from the patient for their anonymized information to be published in this case report.
including demographic data, personal medical information, symptoms and conditions, medical procedures/treatment and recovery, personal genetic information, photos/images. The patient understands that his name will not be released.

**ORCID iD**
Amanda Hamilton [https://orcid.org/0000-0003-1692-5772](https://orcid.org/0000-0003-1692-5772)

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**Appendix I**

*Slides from WLE of left leg and left inguinal sentinel node*

**Image 1.** High-power (x100) magnification of residual MCC within deep dermis and subcutaneous fat of the WLE left leg. Key features of MCC shown with high nuclear to cytoplasmic ratio and hyperchromatic nuclei and stippled chromatin pattern. Stained with H&E staining.
Image 2. Demonstrates small metastatic deposits of MCC with associated large infiltrate of cells within the subcapsular sinus of the left inguinal sentinel lymph node, stained with H&E stain at high power magnification (x100). The largest focus present measured 3 mm. There is at least deposit one present within perinodal soft tissue. Key features demonstrated in images consistent with MCC are cellular arrangement pattern and nuclei have pale chromatin.

Image 3. The left inguinal sentinel lymph node with focus of a 6 mm deposit of metastatic melanoma demonstrating intracytoplasmic melanin, stained with H & E staining at medium power magnification (x40). Consistent with melanoma is the key features of melanocytes associated with blood vessels and large infiltrate of cells with abnormal patterning.

Image 4. Positive staining of WLE of left leg using (a) CK 20 and (b) Synaptophysin.
Image 5. Positive staining of the left sentinel lymph node using (a) CK 20 and (b) Synaptophysin.