Received: 16 February 2022 | Revised: 12 April 2022 | Accepted: 26 April 2022

DOI: 10.1002/ccr3.5891

CASE REPORT

Clinical Case Reports Open Access WILEY

Development of metastatic Merkel cell carcinoma following the excision of same-sided recurrent auricular melanoma

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Funding information
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Abstract

Merkel cell carcinoma (MCC) is a rare neuroendocrine malignancy of the skin that is highly aggressive and often metastasizes early. MCC is diagnosed based on histopathological findings and is most commonly treated with surgical resection, which may be accompanied by chemotherapy and/or radiation. This report describes a 55-year-old male patient with the history of recurrent malignant melanoma of the right pinna and subsequent excision. Three years following the excision of melanoma, he presented with a lesion to the right forehead as well as a right-sided neck mass that were found to be metastatic Merkel cell carcinoma.

KEYWORDS

auricular melanoma, melanoma, Merkel cell carcinoma, second cancer

1 | INTRODUCTION

Merkel cell carcinoma (MCC) is a rare and highly aggressive cutaneous neuroendocrine malignancy that generally presents as a pink to red plaque or nodule on ultraviolet (UV) light-exposed skin.[1] In addition to UV light exposure, other risk factors associated with MCC include older age, fair skin, immunosuppression, and Merkel Cell Polyomavirus (MCPyV) infection.[2] The acronym AEIOU (asymptomatic, expanding rapidly, immunosuppression, older than 50 years, UV-exposed) is useful when clinically characterizing this malignancy.[3]

Diagnosing MCC is challenging as the clinical differential often includes other cutaneous malignancies such as nodular basal cell carcinoma and amelanotic melanoma. Moreover, approximately 30% of Merkel cell carcinomas are misdiagnosed as metastatic small cell carcinoma.[4] Histopathological and immunohistochemical findings are vital in making the diagnosis of Merkel cell carcinoma. Histologically, MCC is characterized by a "small blue round cell tumor" that most frequently involves the dermis and/or subcutis.[5] The cells have a high nuclear-to-cytoplasmic ratio with indistinct nucleoli. MCC cells express several neuroendocrine markers, including chromogranin-A, synaptophysin, cytokeratin 20 (CK20), and CD56.[2] Positive immunohistochemical staining of the aforementioned markers in an identified cutaneous lesion is pathognomonic for Merkel cell carcinoma. A small portion of MCCs (less than 10%) are negative for CK20.[2] These CK20-negative cases have a high mutational burden and are commonly MCPyV-negative. With that being said, 80% of MCC cases are

MCPyV-positive.[5] This virus is ubiquitous among humans with exposure occurring early in life. In MCPyV-positive cases, viral DNA incorporates into the host cell genome, leading to the increased expression of antigenic and oncogenic proteins and subsequent development of cancer. Antibodies against MCPyV have been shown to be increased among older individuals, suggesting that viral reactivation is occurring later in life. In patients with MCPyV-negative MCC, genetic damage by UV exposure is the primary mediator of carcinogenesis.

Management of MCC is guided by appropriate staging. For locoregional disease, treatment includes wide local excision of the primary tumor and resection of regional lymph nodes that may be involved by metastatic disease.[5] Adjuvant radiation therapy is also considered a treatment of choice for locoregional disease, while cytotoxic chemotherapy is primarily reserved for advanced cases. Post-treatment surveillance includes full skin inspection and local lymph node examination every three months for approximately two years, followed by every six months for three years to monitor for disease recurrence.[6] In general, immunosuppressed patients who develop MCC have a worse prognosis than those who are immunocompetent.[5] In addition, there is increased survival in the female sex as compared with males. Notably, MCPyV-positive MCC patients have been found to have a better prognosis than those with MCPyV-negative lesions as well.

2 | CASE PRESENTATION

Our patient is a 55-year-old male patient who was initially referred to the otolaryngology clinic five years ago for the evaluation of a lesion to the right superior pinna. Biopsy of the lesion depicted malignant melanoma of the nodular subtype with a Breslow depth of at least 2.8 mm and margins positive for invasive disease. The patient underwent excision of the melanoma with final pathology reporting negative margins. Two years later, the patient experienced local recurrence of nodular malignant melanoma, which required a 3.5 × 2.6 × 1.8 cm segment of right pinna to be excised. Unfortunately, final pathology of this specimen demonstrated deep margins that were involved by microsatellite lesions of melanoma. The patient then underwent a final operation in which an additional 5.4 × 1.5 × 0.8 cm piece of pinna was removed with margins negative for invasive or in situ disease.

Three years following his last operation, our patient presents with a right-sided neck mass. He reported first noticing the mass approximately two months prior and decided to seek treatment due to the mass seemingly increasing in size. On examination, the mass was firm and immobile. The patient denied any pain, dysphagia, change in voice, or weight loss. He also denied any limitations in lateral head movement. In addition, the patient had a noticeable growth to the forehead, superior to the right eyebrow (Figure 1). The lesion was pink and lobular in nature, first being noticed by the patient approximately 6 months prior to presentation and now measuring 2.5 × 1.7 × 0.7 cm. The patient continued to deny any pain and was more concerned with the right-sided neck mass.

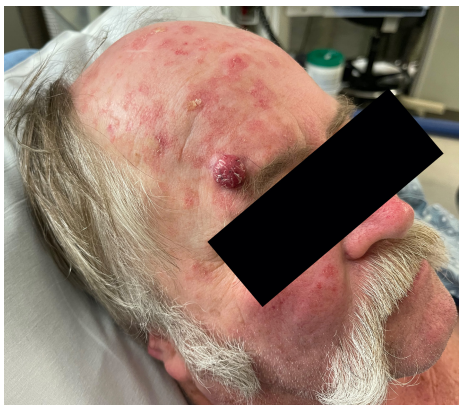

FIGURE 1 Right anterolateral view of the head depicting a lesion directly superior to the patient's right eyebrow

Given the patient's history of recurrent malignant melanoma on the same side, there was an increased suspicion for metastatic melanoma. Ultrasound findings identified a large, hypoechoic mass with poorly defined margins in the right neck (Figure 2), measuring approximately 3.0 × 2.8 × 3.3 cm and corresponding with the palpable mass. There was some peripheral vascularity noted by color Doppler, but there was no increased internal vascularity. Computed tomography of the neck and soft tissue demonstrated a mass similar in size that was most suggestive of a necrotic lymph node concerning for neoplasm.

Ultrasound-guided fine needle aspiration of the patient's right neck mass found loosely cohesive tumor cells with a lymphocyte-predominant background, which was suggestive of metastatic disease involving a lymph node. Several immunohistochemical stains were used to further characterize the neoplasm. The tumor cells were negative for melanoma markers, which included S-100, melan-A, SOX-10, and HMB-45. There was moderate positivity for CKAE1/AE3 and BerEP4, which was supportive of carcinoma. Further staining found the tumor cells to be positive for CD56 (Figure 3A) and synaptophysin (Figure 3B), indicating neuroendocrine differentiation. However, the tumor cells stained negatively for CK20. At this point, the differential included a metastatic neuroendocrine neoplasm of the skin such as Merkel cell carcinoma as well as neuroendocrine neoplasms of other origins such as lung

or gastrointestinal tract. Further evaluation would be necessary to determine the primary tumor site.

The patient underwent a right radical neck dissection, which resulted in the resection of a 13.0 × 8.5 × 4.5 cm mass that contained both tumor and surrounding soft tissue. There was increased adherence of the mass to the right internal jugular vein, which required more delicate dissection. The mass extended superiorly along the right internal jugular vein and was dissected up to the point at which right internal jugular vein passes the inferior edge of the mandible. Because of this, there may have been some microscopic disease remaining on the right internal jugular vein postoperatively. The lesion to the patient's right forehead was also excised during this operation. Final pathology reported the patient's neck mass and forehead lesion to stain positively for both CD56 and synaptophysin, confirming a metastatic high-grade neuroendocrine carcinoma that favored Merkel cell carcinoma and had originated from the patient's right forehead. Pathology also reported the cancer to involve 2 of 21 dissected lymph nodes with extensive involvement of the soft tissue. The excised forehead lesion, however, had negative margins. Due to the patient's metastatic MCC having extensive soft tissue involvement as well as potential for microscopic disease remaining on the right internal jugular vein, he elected to undergo radiation therapy for definitive treatment of his condition.

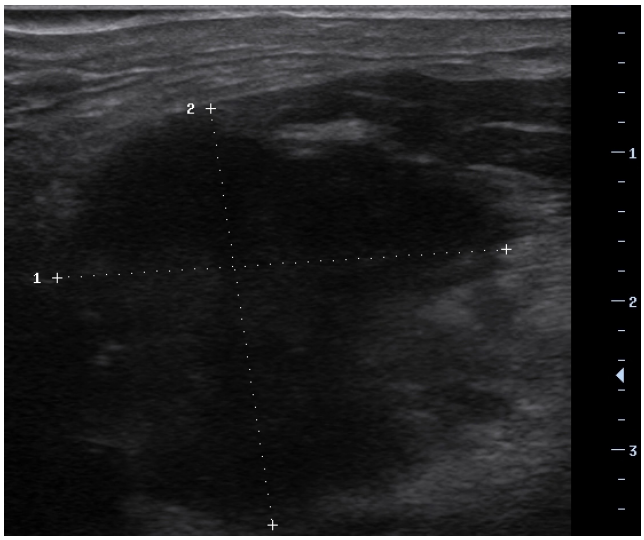

FIGURE 2 Right neck ultrasound depicting a hypoechoic neck mass with poorly defined margins

3 | DISCUSSION

Not to be confused with secondary cancer, a second cancer is a new primary malignancy that develops in an individual months to years after the diagnosis of a different original cancer. Studies have shown that individuals with MCC are at a significantly higher risk of developing second malignancies over a 1-to-5-year period following diagnosis as compared with the general population.[7] Specifically, patients who have been diagnosed with MCC are 52% more likely to develop second cancers after a one-year period. There is an increased risk of developing second malignancies including, but not limited to, colon cancer, breast cancer, non-Hodgkin's lymphoma, and chronic lymphocytic lymphoma following the past diagnosis of Merkel cell carcinoma.[7] Importantly, patients with history of MCC are two times more likely to develop malignant melanoma as a second cancer as compared to other second malignancies. On the other hand, individuals with history of malignant melanoma as a primary cancer have been documented to have a 9-fold increased risk of developing malignant melanoma as a second cancer later in life.[8] Melanoma survivors have also been shown to have an increased risk of developing other cancers such as breast cancer, prostate cancer, and non-Hodgkin's lymphoma.

There have been reports describing the development of malignant melanoma following the treatment of MCC, but reports documenting the development of MCC following the excision of malignant melanoma are scarce.[9] Interestingly, there has been a report of a patient who was incidentally found to have both metastatic MCC and metastatic melanoma in a single sentinel lymph node

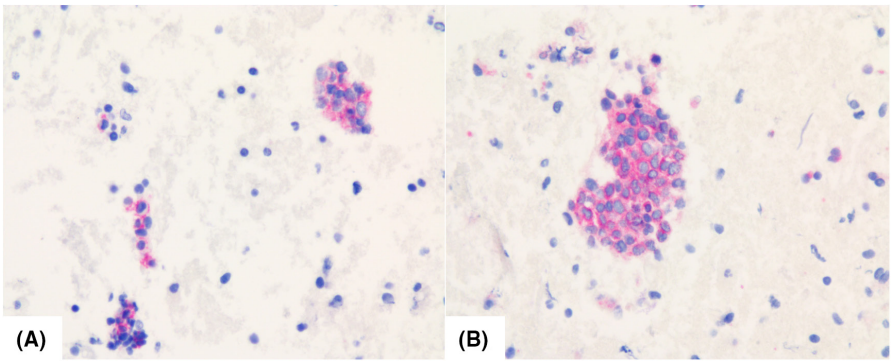

FIGURE 3 Cytopathology of right neck mass aspirate. (A) Aspirate cells demonstrating positivity for CD56. (B) Aspirate cells demonstrating positivity for synaptophysin

following wide local excision of Merkel cell carcinoma.[10] Regardless, the development of MCC as a second cancer to malignant melanoma is underreported.

Recent studies have identified cases of MCPyV-positive melanoma.[11] As compared with MCPyV-positive MCC, these cases exhibited different pathogenic oncoprotein variants. Mutations identified in virus-positive MCC include *RB1*, *TP53*, *FBXW7*, *CTNNB1*, and *HNF1A*, while *BRAF*, *PIK3CA*, *STK11*, *CDKN2A*, *SMAD4*, and *APC* were identified in virus-positive melanoma. It is well-established that there is a higher tumor burden in patients with MCPyV-positive MCC as compared with virus-negative cases; however, no association has been found between MCPyV infection and tumor burden in melanoma.

In the case of our patient, his melanoma lesions were not screened for MCPyV as this screening is not indicated in the diagnosis and treatment of cutaneous melanoma.[12] There was no suspicion of MCPyV involvement due to its rarity in melanoma lesions, and furthermore, the patient had not yet presented with MCC. By the time our patient had presented with MCC, his disease had already metastasized to the right cervical nodes. The patient's MCC was not screened for MCPyV because at that time, the priority was surgical resection of his metastatic disease. Although the patient's MCC was CK20-negative and suggestive of MCPyV-negative cancer, the probability of MCPyV involvement remains high. The patient continues to undergo thorough physical examination of skin and regional lymph nodes, and in the case of recurrent MCC or malignant melanoma, will undergo MCPyV screening.

We write this report to emphasize that although rare, Merkel cell carcinoma should not be overlooked as a second cancer, especially in individuals with history of malignant melanoma. MCC remains an incredibly aggressive malignancy that often metastasizes quickly and requires early treatment.

4 | CONCLUSION

Although there have been reports describing the development of second cancers following the treatment of MCC, the development of MCC after the treatment of other malignancies has not been well-described. While the patient described in this report was not screened for MCPyV at the time of MCC presentation, screening for the virus could be clinically useful, especially when considering the recently reported melanoma cases that were also found to be MCPyV-positive. Merkel cell carcinoma is a very rare skin cancer, but it should not be excluded from the differential when evaluating a patient with history of non-MCC cutaneous malignancy who presents with a new skin lesion and possible metastatic disease.

AUTHOR CONTRIBUTIONS

Jake K. Cartwright wrote the original draft of this report in addition to conceptualizing the project and making subsequent revisions. Daniel H. Snyder contributed to project design and assisted in revision. Francisco G. Moreno contributed to project design, assisted in revision, and supervised the overall production of this report.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

The authors declare that there are no competing financial or personal interests that may have influenced the production of this case report.

DATA AVAILABILITY STATEMENT

All data used in this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

East Tennessee State University IRB was consulted and confirmed that IRB approval was not required for this study.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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How to cite this article: Cartwright JK, Snyder DH, Moreno FG. Development of metastatic Merkel cell carcinoma following the excision of same-sided recurrent auricular melanoma. *Clin Case Rep*. 2022;10:e05891. doi:10.1002/ccr3.5891