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Case Report

Bilateral symmetric Merkel cell carcinomas of the dorsal hands: multiple primary tumors or early metastasis?

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ABSTRACT

Merkel cell carcinoma (MCC) is an aggressive and uncommon neuroendocrine tumor which clinically presents as a rapidly growing solitary nodule or plaque located in sun exposed areas on the head, neck, and extremities. Merkel cell carcinomas can be UV-induced or result from viral infection with the Merkel cell polyomavirus (MCV). We present a unique case of bilateral symmetric Merkel cell carcinomas located on the dorsal hands and briefly discuss options for genomic investigation to delineate if the tumors are multiple primary tumors or result of metastatic disease.

Keywords: MCC, MCV, Neuroendocrine tumor, Cytokeratin-20

INTRODUCTION

Merkel cell carcinoma (MCC) is an uncommon, aggressive neuroendocrine tumor with a poor prognosis which clinically presents as a solitary rapidly growing violaceous nodule or plaque, typically located on the head, neck, or other sun-exposed areas.[1] We present a unique case of concomitant bilateral symmetric MCCs located on the dorsal hands, leading to a diagnostic challenge differentiating bilateral symmetric primary MCCs or a primary MCC metastatic symmetrically to the contralateral hand.

CASE REPORT

A healthy 88-year-old male with history of multiple non-melanoma skin cancers presented for consultation for Mohs micrographic surgical management of a previously biopsied MCC of the left 4th digit (Figure 1). A firm violaceous nodule was noted atop the left dorsal proximal phalange, and further clinical inspection revealed a contralateral symmetric nodule overlying the right 4th metacarpal joint (Figure 2) and no palpable lymphadenopathy. Biopsy of the newly identified lesion was obtained and similarly demonstrated dermal islands of blue cells with multiple mitotic figures (Figures 3 to 5). Differential diagnosis included bilateral symmetric primary MCCs, metastatic MCCs, metastatic small cell lung carcinoma, and metastatic neuroendocrine carcinoma from another organ. Immunohistochemical staining was positive for cytokeratin-20 (Figure 6) and neuron specific enolase (NSE), and negative for thyroid transcription factor-1 (TTF-1), consistent with MCC. Initial PET/CT and repeat imaging at 2 months were negative. Sentinel node biopsy was not performed given imaging results. This unique clinical presentation led to a diagnostic conundrum, with histopathology and imaging narrowing the diagnosis to bilateral symmetric primary MCCs or a primary MCC metastatic symmetrically to the contralateral hand. The patient was managed with Mohs micrographic surgery followed by radiation. Due to financial restrictions, further genomic testing could not be performing to further classify the tumors or identify viral positivity. The patient is currently closely monitored by

both dermatology and oncology without evidence of recurrence or development of new primary lesions.

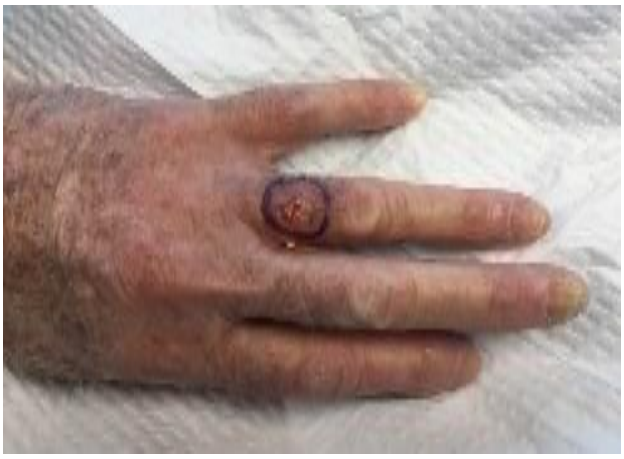

Figure 1: Merkel cell carcinoma presenting as a violaceous ulcerated nodule overlying the left 4th proximal digit.

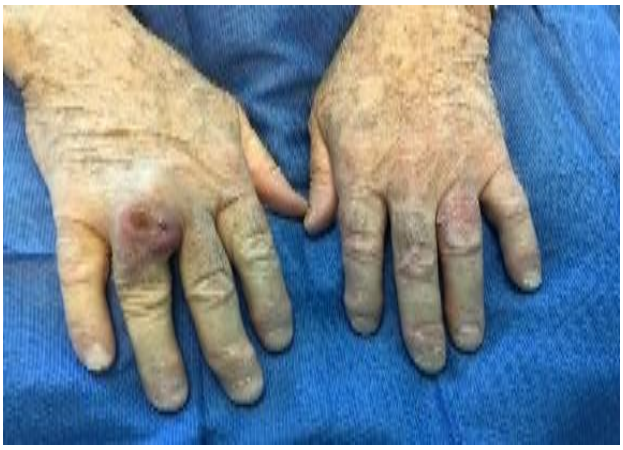

Figure 2: Violaceous ulcerated nodule overlying the right 4th metacarpal joint and well healed Mohs surgical site repaired with a full thickness skin graft on the left 4th proximal digit.

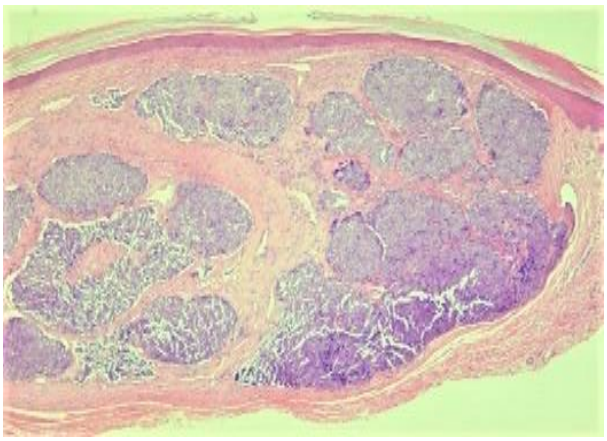

Figure 3: Nodular dermal infiltrate of small, round basaloid cells with mitotic figures, (H and E, 2x).

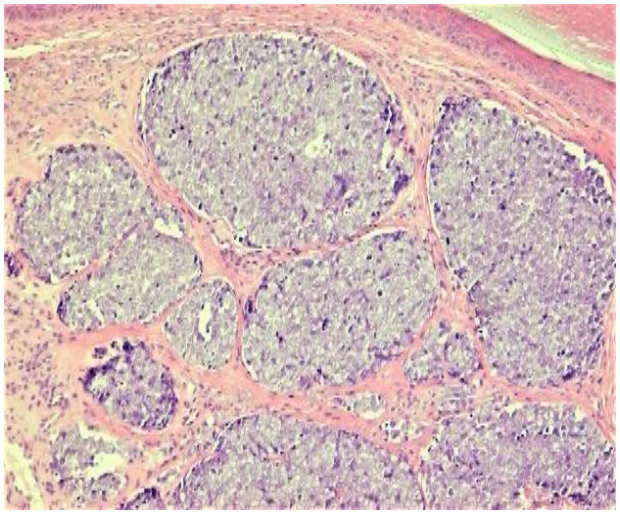

Figure 4: Nodular dermal infiltrate of small, round basaloid cells with mitotic figures, (H and E, 10x).

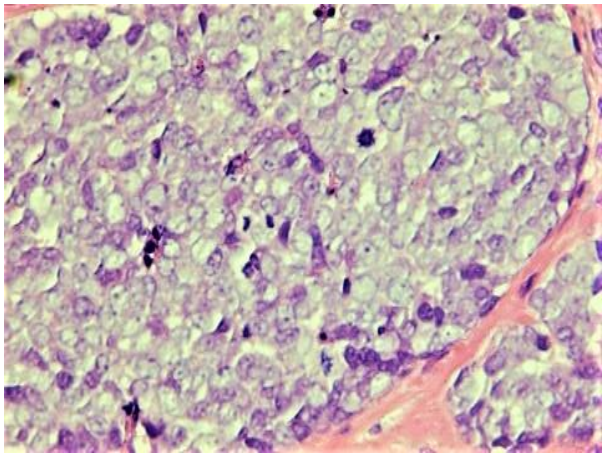

Figure 5: Nodular dermal infiltrate of small, round basaloid cells with mitotic figures and several apoptotic cells (H and E, 40x).

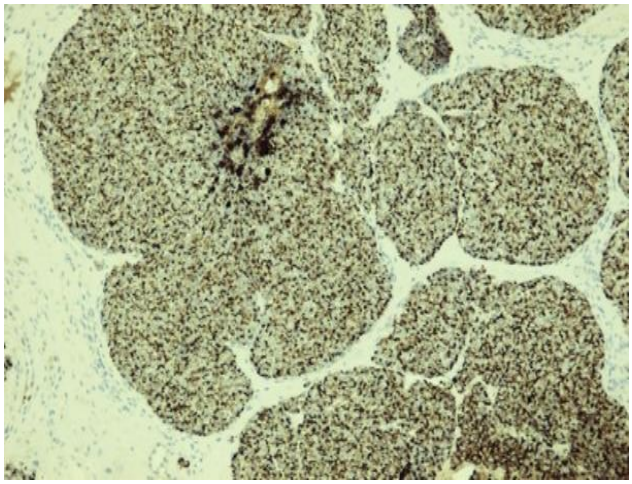

Figure 6: Cytokeratin-20, 10x: CK-20 immunohistochemical staining demonstrating perinuclear dot pattern.

DISCUSSION

MCC is an uncommon, aggressive primary cutaneous neuroendocrine malignancy which favors the head and neck of Caucasian men >65 years of age.[1,2] Epidemiologic studies have identified risk factors to include sun exposure, fair skin, advanced age, and immunosuppression.[1] The understanding of the origins and pathogenesis of MCC is still evolving and likely involves multipart interaction between genetics, UV exposure, viral infection, and immunosuppression. MCV was first reported in association with MCC in 2008 and infects approximately 80% of MCC.[3,4] This oncogenic double stranded DNA virus integrates into the host genome and may contribute to tumorigenesis of MCC. Given the propensity of MCC to occur in areas of sun exposure, it has been hypothesized that mutations in the viral genome that drive oncogenesis may be induced by UV radiation, and local immune system evasion may allow for cellular proliferation.[5]

Clinically MCC presents as a solitary rapidly growing violaceous nodule or plaque, typically located on the head, neck, or other sun-exposed areas.[1] These tumors can mimic benign growths including inflamed cysts or scars, and other cutaneous malignancies including non-melanoma skin cancers and melanomas. As with our patient, unusual clinical presentations can occur, so MCC should be included in the differential diagnosis of lesions that are rapidly growing or do not respond to expected classical treatment.

Diagnostic evaluation of MCC includes clinical examination of the skin and lymph nodes, biopsy of suspicious lesions, and histopathologic assessment. On histopathologic evaluation MCC is characterized as a basaloid dermal tumor with nests and sheets of cells with granular chromatin pattern, mitotic figures, and scant cytoplasm.[6] MCC is characteristically positive for CK-20 in both a diffuse cytoplasmic and a paranuclear dot pattern, synaptophysin, chromogranin, CD56, and neuron specific enolase. TTF-1 is typically negative in MCC, but positive in metastatic small cell lung carcinoma.[6]

Once the diagnosis of MCC has been established, further evaluation and staging should be performed based on the national comprehensive cancer network (NCCN) guidelines and may include clinical lymph node evaluation, sentinel lymph node biopsy (SLNB), imaging studies like MRI or PET/CT, and multidisciplinary consultation.[7] As with our patient, when multiple tumors are present or when new tumors emerge over time, additional genomic testing can be performed to help differentiate multiple primary tumors verses metastatic disease. Microarray-based comparative genomic hybridization (aCGH), next generation sequencing (NGS), whole exome sequencing (WES), whole genome sequencing (WGS), and RNA hybridization assays can be used to delineate mutations, alterations, and structural variations amongst tumors to compare for similar aberrations and viral positivity. MCV serology test (AMERK) detects circulating antibodies against MCV and can be obtained at baseline then serially onward to aid in detection of MCC recurrence.[8-14]

The American joint committee on cancer (AJCC) updated the staging system for MCC in 2017. MCC has a poor prognosis with overall survival at 5 years is approximately 51% for local disease, 35% for nodal disease, and 14% for distant disease.[15]

Given the complex aggressive behavior of MCC, these tumors are best managed by a multidisciplinary team. Treatment options are individualized, but may include monotherapy or combinations of wide local excision, Mohs micrographic surgery (MMS), radiation, and chemotherapy.[16] Emerging investigational therapeutic immunotherapy agents include the programmed death receptor-1 (PD-1)/programmed death ligand-1 (PD-L1) pathway inhibitors, pembrolizumab and avelumab, and the cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) inhibitor, ipilimumab.[16] Targeted molecular therapy agents under investigation include somatostatin analogs, tyrosine kinase inhibitors, and mTOR inhibitors.[16] Given a poor prognosis with high risk of recurrence, metastasis, and death, patients should undergo close surveillance with clinical evaluation every 3 months and routine surveillance imaging. Patient was managed with surgical removal of both lesions via MMS and is currently undergoing adjuvant radiation therapy with close interdisciplinary surveillance by general dermatology and oncology. The advantage of MMS is complete deep and peripheral margin control while conserving healthy tissue on functionally sensitive area like the hand.

CONCLUSION

In conclusion, we present a unique case of bilateral symmetric MCC leading to a diagnostic conundrum, with histopathology and imaging narrowing the diagnosis to bilateral symmetric primary MCCs or a primary MCC metastatic symmetrically to the contralateral hand. Numerous genetic tests are emerging and can be used to further evaluate multiple tumors to distinguish if they are multiple primary tumors or metastatic in nature, which may impact staging and treatment options. Although therapeutic options are rapidly emerging, treatment is difficult with high rates of recurrence, metastasis, and mortality, prompting the need for swift diagnosis, staging, and development of an individualized multidisciplinary therapeutic approach.

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