A case report of 2 patients developing multiple Merkel cell carcinomas—using comparative genomic hybridization to elucidate tumor relationship

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Key words: comparative genomic hybridization; fine-needle aspiration; Merkel cell carcinoma; oligometastatic spread; positron emission tomography/computed tomography; sentinel lymph node biopsy; wide local excision.

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare cutaneous malignancy of neuroendocrine differentiation typically found on the head and neck of sun-exposed patients with fair skin. The disease is characterized by an aggressive course with frequent metastasis.[1] Survival is approximately 51% at 5 years for localized disease and as low as 14% with distant disease, which underscores the importance of prompt diagnosis and management.[2]

Examples of individual patients diagnosed with multiple primary cutaneous MCCs are rare and there are few published case reports. Thus, the prevalence of multiple MCC primary cutaneous tumors is unknown. Furthermore, it is hypothesized that some early reports of multiple cutaneous primary MCCs may represent in-transit or distant metastases, given the lack of confirmatory sequencing of tumor genetic signatures.[3]

Comparative genomic hybridization (CGH) is a genetic testing method used to identify segmental chromosome deletions and duplications in cancer cells. Historically, the genetics of MCC were poorly characterized; however, application of CGH to MCCs has identified several candidate genes in MCC pathogenesis.[4] Recently, novel copy number changes of chromosomes identified through CGH have been used to determine if dispersed cutaneous MCC have arisen *de novo*, or if they represent the same primary tumor with subsequent isolated cutaneous metastasis, or oligometastatic spread.[5]

Here we present our institution's experience with multiple cutaneous MCCs. In both of these cases, CGH analysis was used to determine tumor relationship and guide management.

Abbreviations used:

CGH:	comparative genomic hybridization
MCC:	Merkel cell carcinoma
PET/CT:	positron emission tomography/computed tomography
WLE:	wide local excision

CASE REPORT

Case 1

A 74-year-old man presented with a subcutaneous nodule on the lower portion of the left side of the back. A fine-needle aspiration was performed, which rendered a diagnosis of MCC. A sentinel lymph node biopsy was negative for metastasis, and there was no distant metastatic disease based on positron emission tomography/computed tomography (PET/CT). The patient underwent wide local excision (WLE) with adjuvant radiation to the lower portion of the left side of the back, 50 Gy in 25 fractions.

One year later, the patient presented with a subcutaneous mass of his left thigh, which was diagnosed as MCC via fine-needle aspiration. The patient again underwent WLE. A repeat PET/CT confirmed a hypermetabolic mass of the thigh, but it was otherwise unremarkable.

Two years after initial presentation, the patient was diagnosed with a third MCC on the lower portion of the right side of the back. At this time, CGH was performed on all specimens, showing a

From the Department of Dermatology, University of California.
Funding sources: None.
IRB approval status: Not applicable.
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JAAD Case Reports 2022;22:21-3.
2352-5126

https://doi.org/10.1016/j.jdcr.2022.01.018

gain in chromosomes 11 and 6q, a loss in distal chromosome 3q (left part of the back), a possible gain in chromosome 2q, a clear loss in chromosomes 13q and 14q (thigh), a gain in chromosome 5p, and a loss in chromosomes 3, 4, 5q, and 10 (right side of the back). The unique CGH profiles confirmed that these lesions represented 3 unique primary tumors rather than metastases. The third primary tumor of the lower portion of the right side of the back was treated with WLE alone. There was no evidence of disease during the 10-year follow-up period.

Case 2

An 86-year-old man presented with an MCC of the right elbow. The tumor was excised with 2-cm margins, and sentinel lymph node biopsy was negative for metastases. No distant metastatic disease was identified by PET/CT. He received adjuvant radiation to the primary site, 50 Gy in 25 fractions. One year later, the patient represented with an enlarging lesion on his right cheek, which revealed the same diagnosis. Again, the patient underwent WLE, with negative sentinel lymph node biopsy. He received adjuvant radiation to the primary site, 50 Gy in 25 fractions. Three years after the initial presentation, the patient was diagnosed with a third MCC of his upper portion of the left eye. A sentinel lymph node biopsy was negative for metastasis, and no distant metastatic disease was observed on PET/CT. The patient is currently undergoing radiation monotherapy to the eyelid. CGH was performed on all specimens, revealing a loss in chromosomes 7q and 17p (right elbow), a gain in chromosome 6p, a loss in chromosomes 14q (right cheek), and a loss in chromosome 8p (left eyelid). The unique CGH profiles demonstrate that these lesions represented 3 unique primary tumors rather than metastases.

DISCUSSION

MCC is a rare diagnosis, with some studies estimating that the overall age-adjusted worldwide incidence ranges from 0.10 to 1.6 cases per 100,000 individuals per year. To put this into perspective, for each MCC diagnosed annually, there are approximately 33 melanomas.[2] Diagnosing multiple MCCs in one patient is an even rarer event; the prevalence of multiple MCC primary cutaneous tumors is unknown.

Most additional tumors occur within the first 2 years of initial MCC diagnosis.[6] MCC is understood to metastasize primarily via the lymphatics rather than via blood. The draining lymph node basin is the most common first site of metastasis,[6] and approximately 25% to 30% of patients with a negative lymph node examination have lymph node micrometastases at the time of presentation.[2] In addition to the draining lymph node basins, prior case report data show metastases to distant skin, lung, central nervous system, bone and liver.[3] Although systemic metastases were believed to have no specific distant predilection site, in one study reviewing 20 years of imaging data, the liver and lungs were the most affected solid organs, whereas distant lymph nodes represented the most common site overall.[6]

There have only been a few cases in which CGH was used to differentiate metastases from multiple cutaneous primary MCCs, when a second cutaneous lesion is diagnosed at a distant site (Table 1). In 2002, Nagy et al[5] demonstrated that 2 MCCs on the palatine tonsil and lip shared copy number changes at 45 chromosomal loci, and thus represented metastases. In 2017, Eluri et al[7] utilized CGH to determine that there were no copy number aberrations between a nose and an arm MCC, thus concluding that these 2 tumors represented separate primary cutaneous MCC.

At our institution, as previously reported by Ahronowitz et al in 2011,[3] CGH findings were consistent with a primary cheek MCC with hematogenous spread and resulting cutaneous metastasis of the contralateral lower extremity. The additional patients we are now reporting (*Case 1* and *Case 2*) with cutaneous MCCs add to the sparse literature in which CGH has been used to evaluate tumor relationships among multiple MCCs diagnosed in a single patient. In both of these cases, the chromosomal changes identified in the first tumor were not present in the second or third tumor, and the chromosomal changes identified in the second tumor were not present in the third tumor. These CGH data suggest that these tumors do not represent metastases but rather 3 separate primary cutaneous MCCs.

Although CGH has largely been replaced by next-generation sequencing in precision oncology, some common chromosome gains/losses identified in MCC in other studies should be worth mentioning. Van Gele et al[8] performed CGH on 34 tumor specimens from 24 different patients and observed gains for chromosomes 1, 3q, 5p, 8q, 19, and X, and losses for chromosomes 3p, 5q, 8p, 10, 11q, 13q, and 17p. Overall, there appears to be a gain of chromosome 5p, as well as a loss of chromosomes 3, 8p, 13q, and 17p in both the study reported by Van Gele et al[8] and in at least one other tumor reported in Table I Further investigation is required to determine if these similarities are statistically significant.

Conclusively, the cases in the existing literature combined with these new cases highlight the ability to clinically distinguish multiple primary cutaneous

Table I. An overview of the results of the 2 cases presented as well as known prior case reports that have utilized CGH to determined possible MCC oligometastatic spread

Manuscript	Tumor location	CGH concordance	Tumor relationship
Lowenstein et al.			
Patient 1	Lower portion of the left side of the back, left thigh, lower portion of the right side of the back	Lower portion of the left side of the back: Gain of 11, 6q; loss of 3q Left thigh: Gain of 2q; loss of 13q, 14q Lower portion of the right side of the back: Gain of 5p; loss of 3, 4, 5q, and 10	Multiple primaries
Patient 2	Right elbow, right cheek, left eyelid	Right elbow: Loss of 7q and 17p Right cheek: Gain of 6p; loss of 14q Left eyelid: Loss of 8p	Multiple primaries
Previous case reports			
Ahronowitz et al (2011)*,[3]	Lower portion of the right eyelid, Lower portion of the left leg	Both tumors: Gain of 12p; loss of 8p, 17p	Single primary
Nagy et al (2005)[5]	Upper portion of the lip, palatine tonsil	Both tumors: Gain of 2p and 10p; loss of regions of 1, 2, 3, 17, 18	Single primary
Eluri et al (2017)[7]	Nasal bridge, left arm, right side of the nose	Left arm, right nose: No significant overlap observed	Mutiple primaries

CGH, Comparative genomic hybridization.
*This case was previously reported by our institution.

MCC from oligometastatic spread. Hence, CGH profiles on multiple tumors from the same patient guide therapeutic decisions.

Conflicts of interest

None disclosed.

REFERENCES

1. Yom SS, Rosenthal DI, El-Naggar AK, Kies MS, Hessel AC. Merkel cell carcinoma of the tongue and head and neck oral mucosal sites. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2006; 101(6):761-768. https://doi.org/10.1016/j.tripleo.2005.10.068
2. Coggshall K, Tello TL, North JP, Yu SS. Merkel cell carcinoma: an update and review: pathogenesis, diagnosis, and staging. *J Am Acad Dermatol*. 2018;78(3):433-442. https://doi.org/10.1016/j.jaad.2017.12.001
3. Ahronowitz IZ, Daud AI, Leong SP, et al. An isolated Merkel cell carcinoma metastasis at a distant cutaneous site presenting as a second 'primary' tumor. *J Cutan Pathol*. 2011;38(10):801-807. https://doi.org/10.1111/j.1600-0560.2011.01757.x
4. Paulson KG, Lemos BD, Feng B, et al. Array-CGH reveals recurrent genomic changes in Merkel cell carcinoma including amplification of L-Myc. *J Invest Dermatol*. 2009;129(6): 1547-1555. https://doi.org/10.1038/jid.2008.365
5. Nagy J, Fehér LZ, Sonkodi I, Lesznyák J, Iványi B, Puskás LG. A second field metachronous Merkel cell carcinoma of the lip and the palatine tonsil confirmed by microarray-based comparative genomic hybridisation. *Virchows Arch*. 2005;446(3):278-286. https://doi.org/10.1007/s00428-004-1176-0
6. Kouzmina M, Koljonen V, Leikola J, Böhling T, Lantto E. Frequency and locations of systemic metastases in Merkel cell carcinoma by imaging. *Acta Radiol Open*. 2017;6(3): 2058460117700449. https://doi.org/10.1177/2058460117700449
7. Eluri M, Feneran A, Bordeaux JS, et al. Multiple Merkel cell carcinomas: late metastasis or multiple primary tumors? A molecular study. *JAAD Case Rep*. 2017;3(2):131-134. https://doi.org/10.1016/j.jdcr.2017.01.011
8. Van Gele M, Speleman F, Vandesompele J, Van Roy N, Leonard JH. Characteristic pattern of chromosomal gains and losses in Merkel cell carcinoma detected by comparative genomic hybridization. *Cancer Res*. 1998;58(7):1503-1508.