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Microsatellitosis in Merkel cell carcinoma: a staging quandary

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To the Editor:

Merkel cell carcinoma (MCC) is a rare small cell cancer of the skin with a high rate of metastasis and mortality. Although microsatellite disease—disease deposits in close proximity to, yet discontinuous from, the site of the primary tumor and revealed only on pathological assessment—has been characterized as an adverse prognosticator in melanoma, its significance has not yet been established in MCC [1]. We investigated the frequency of microsatellite disease in a 5-year cohort of patients with primary cutaneous MCC by reviewing pathology reports available from the Mass General Brigham electronic medical record and examined the real-world staging decisions made in these situations [2]. Of 213 patients, only 6 cases (2.8%) were clearly described as featuring microsatellite disease at presentation (**Table 1**). Of these cases, four were upstaged to Stage IIIB disease in the absence of any further metastasis, whereas one patient with microsatellite disease was classified as "local" or "Stage I" disease. The cases displayed variability in the size, number, and depth of the microsatellites (**Table 1**).

According to the American Joint Committee on Cancer (AJCC) 8th edition staging criteria for MCC, the presence of in-transit metastases upstages disease to N2 or N3 nodal category and overall Stage IIIB disease [3]. "In-transit" metastasis is defined as a catch-all category for describing metastatic intralymphatic deposits either distal to the primary tumor or en route to the regional nodal basin [3]. In our experience, in-transit metastases are typically clinically appreciable. However, both the AJCC 8th edition staging criteria and latest National Comprehensive Cancer Network (NCCN) management guidelines do not specifically address handling of MCC disease presenting with microsatellites, and outcomes data are not available to guide prognostication in this subset of cases [3,4]. Our review suggests that these cases may be frequently upstaged to Stage IIIB disease, indicating that clinicians might be using melanoma staging conventions as a reference in real-world practice. In contrast to the MCC guidelines, the AJCC 8th edition guidelines for melanoma do define a microsatellite category, with reportedly no "substantial" difference in survival outcomes between presentations with microsatellites, satellites (grossly detectable deposits <2cm from the primary tumor), and in-transit metastases (deposits >2cm removed from the primary tumor) in the AJCC 8th edition melanoma outcomes database [5]. Moreover, a 2020 study of 69 confirmed cases of microsatellite disease in melanoma with matched controls indicated significantly worse outcomes in the setting of microsatellites including overall and disease-specific survival, sentinel node positivity, and locoregional recurrence; interestingly, distance from the microsatellite to the primary tumor, but not number or size of microsatellites, was found to be prognostically significant [6]. No similar literature

exists for MCC of which we are aware, likely related to the challenges in sufficiently powering such investigations.

Upstaging MCC cases with microsatellites to Stage IIIB disease places them in a cohort with a 5-year overall survival of 26.8% (23.4-30.4), [3]. Although it is unclear whether these staging decisions result in altered management or surveillance—decisions on adjuvant therapies and surveillance schedules take into account the totality of tumor histopathology and the patient's clinical outlook—at a minimum, upstaging has significant impact on physician-patient discussions on prognosis. Although melanoma has historically served as a reference disease for MCC, a rare tumor for which consensus staging guidelines were published only 10 years ago, the significance of microsatellite disease in MCC continues to be poorly understood. Given the rarity of this presentation in MCC, further investigations powered by multi-institutional datasets exploring associations between microsatellite presence and other adverse pathological predictors, locoregional and distant recurrence, and survival outcomes are needed.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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Table 1. *Clinical and pathological features of cases of Merkel cell carcinoma with microsatellitosis.*

No.	Location of primary tumor	Greatest clinical size of primary tumor (cm)	Clinical extent of disease	Greatest pathological size of primary tumor (cm)	Size of largest microsatellite (mm)	Number of microsatellites	Location of microsatellites	Sentinel node outcome	Highest clinician recorded pathological stage	Initial/adjuvant treatments	First recurrence	Total follow-up time (days)
1	Head/Neck	2	Local	1.7	6	Multiple	Dermis	Positive	IIIB	Definitive Excision	Local, Regional	442
2	Buttocks	2.2	Local	1.9	"microscopic"	Single	Subcutaneous Fat	Negative	I	Definitive Excision, Primary Site Radiation[a]	(-)	1137
3	Upper Extremity	2.6	Local	1.1	3	Multiple	(-)	Negative	IIIB	Excisional Biopsy, Definitive Excision, Primary Site Radiation	(-)	1346
4	Upper Extremity	1.2	Local	1	(-)	Multiple	Dermis	(-)	IIIB	Definitive Excision, Primary Site Radiation	(-)	181
5	Trunk	3.1	Local	4	(-)	Multiple	(-)	(-)	IIIB	Definitive Excision	Regional	141
6	Upper Extremity	1.3	Local	(-)	3	Single	Subcutaneous Fat	Negative	IIIB	Excisional Biopsy, Definitive Excision, Primary Site Radiation, Systemic Therapy	(-)	436