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Letter to the editor

# Complete response with neoadjuvant avelumab in Merkel cell carcinoma – A case report

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ABSTRACT

Merkel cell carcinoma (MCC) is a rare but aggressive neuroendocrine skin malignancy. We report here a case of localized MCC achieving pathologic complete response upon treatment with avelumab in the neoadjuvant setting. Preclinical and clinical studies have revealed a close relationship between MCC and the immune system, thus supporting a role for PD-1/PD-L1 inhibitors in MCC. This neoadjuvant use of PD-1/PD-L1 inhibitors can avoid potentially disfiguring surgery in MCC. As the incidence of MCC is rising, clinical trials are needed to evaluate the efficacy and safety of immunotherapy in resectable disease.

## Background

Merkel cell carcinoma (MCC) is a rare neuroendocrine cutaneous carcinoma. It has the worst prognosis among the different types of cutaneous neoplasms including melanoma [1]. MCC is common in white, male, elderly and immunocompromised individuals [2]. The majority of MCC cases are linked to infection with the Merkel cell polyoma virus (MCPyV), while the remaining cases are attributed to UV-induced mutations [3,4]. At presentation, disease is limited to the primary tumor in approximately 65% of cases. Nodal involvement is present in 26%, and distant metastases in 8% [5].

The primary treatment for localized disease is surgery with or without adjuvant radiotherapy. Although MCC is sensitive to chemotherapy, responses are not durable, with median progression-free survival (PFS) of about 3 months [6] and there are currently no established standard treatment for advanced disease. Based on data from the surveillance, epidemiology, and end results (SEER) registry, the incidence of MCC has increased from 0.22 to 0.79 per 100,000 person years from 1986 to 2011 [7]. It is predicted that MCC incidence in the US will continue to increase, to reach a projected 3284 cases/year in 2025, as compared to 2488 cases/year in 2013 [8].

Clinical trials have shown objective and durable responses with PD-1/PD-L1 inhibitors in advanced MCC which has led to the inclusion of avelumab, pembrolizumab and nivolumab in the national comprehensive cancer network (NCCN) treatment guidelines for advanced MCC [9]. Although study results for PD-1/PDL-1 inhibitors in metastatic MCC are promising [10–12], there is little data on the efficacy of checkpoint inhibitors in the neoadjuvant setting [13]. We report here a case of a patient with localized MCC who achieved pathologic complete response when treated with avelumab in the neoadjuvant setting.

## Case presentation

A 90-year-old man presented with a right cheek mass. Pathology from the punch biopsy was consistent with MCC, at least Clark's level IV, with a tumor thickness of 3.5 mm. Peripheral and deep margins were positive (Fig. 1A). CT scan showed a 0.9 × 0.6 cm enhancing cutaneous/subcutaneous nodule overlying the accessory parotid gland without infiltration. He was offered wide local excision with sentinel lymph node biopsy, but was deemed a high risk surgical candidate due to his advanced age and carotid atherosclerosis. He ultimately opted for non-surgical treatment. Avelumab was given at a dose of 10 mg/kg every 2 weeks of 4 weeks cycle. Interval CT scan after 2 cycles showed a decrease in size of the lesion to 0.8 × 0.3 cm. After 4 cycles, he underwent local excision of the persistent lesion with a 1 cm margin. The lesion was localized intraoperatively by ultrasound. Surgical pathology revealed complete response with no evidence of residual MCC (Fig. 1B).

## Discussion

In recent years, PD-1/PD-L1 inhibitors have shown remarkable responses in multiple advanced tumors including MCC. The earliest results came from a phase 2 study where pembrolizumab achieved an objective response rate (ORR) of 56% in treatment naïve stage IV and unresectable stage IIIB MCC [12]. In an updated analysis, the ORR was 44–52% and 18 months overall survival (OS) was 68% [14]. In the phase 2 JAVELIN Merkel 200 trial, avelumab achieved ORR of 33% in chemotherapy refractory stage IV MCC. Median OS was 12.6 months [10,15,16]. In the first line setting for metastatic MCC, avelumab achieved an ORR of 62.1% [11,17].

The phase 1/2 checkmate 358 trial provided the first evidence of response to PD-1 inhibitors in the neoadjuvant setting. Nivolumab was used to treat patients with stage IIA-IV MCC, achieving tumor regression in 16 of 20 patients (80%). A major pathologic response was seen in 11 of 17 tumor resections (65%), including complete responses in 8. At 12 months, only 2 of 21 operated patients had relapsed [13].

Preclinical and clinical studies have revealed a close relationship between MCC and the immune system. Immunosuppression is an established risk factor for MCC, and incidence is higher in patients with chronic lymphocytic leukemia, HIV, and in organ transplant recipients

*Abbreviations:* MCC, Merkel cell carcinoma; MCPyV, Merkel cell polyoma virus; NCCN, national comprehensive cancer network; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SEER, surveillance, epidemiology, and end results

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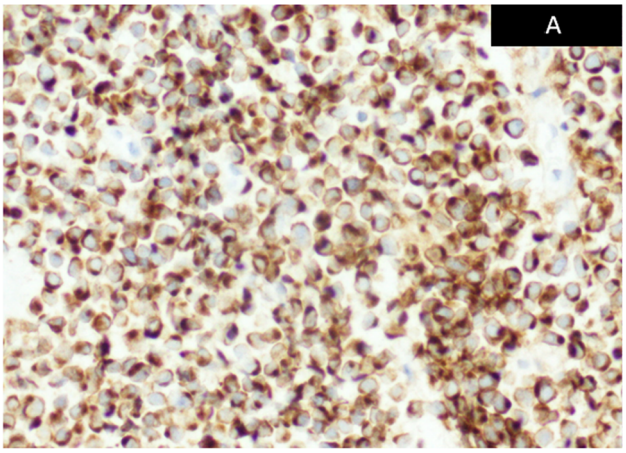


**Fig. 1.** (A). Punch biopsy of the right cheek mass. Staining for CD20 showed a Golgi localized pattern (dot-like staining), characteristic of neuroendocrine cells. 400×. (B). The resection specimen demonstrated chronic inflammation with dermal edema in the reticular dermis. No evidence of malignancy was found. 10×.

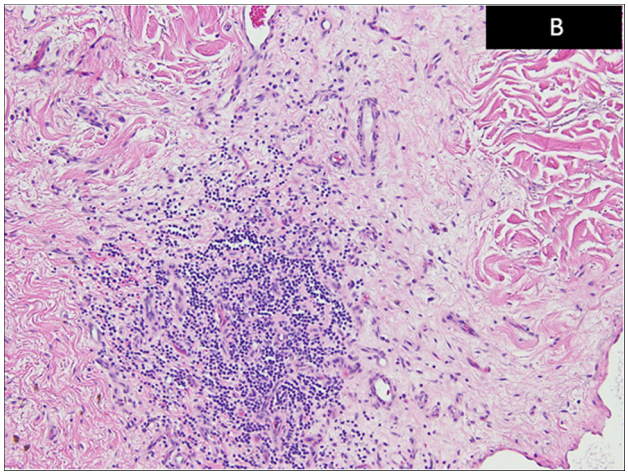


**Fig. 1.** (*continued*)

[2]. The increased incidence in older patients has also been linked, at least in part, to age-induced immunosuppression. Immunosuppression has been shown to predict reduced MCC-specific survival independent of disease stage [18]. Conversely, intra-tumoral CD8+ cell infiltration has been shown to be a predictor of improved MCC-specific survival [19]. Reversal of the immunosuppressed state has the potential to induce tumor regression [20]. Additionally, there have been reports of spontaneous tumor regression, suggesting immune clearance [21]. Similarly, improved OS has been reported with MCC without a concurrent primary lesion, which may reflect immune clearance at the primary site [5,22]. The majority of MCC cases are linked to infection with MCPyV, while the remaining cases are attributed to UV-induced mutations. These two causes contribute to a large mutational load and create neoantigens, inducing robust innate and adaptive immune responses and recruiting inflammatory cells to the tumor microenvironment [23,24]. Specifically, the mutational burden of virus negative MCC tumors exceeds that of other tumors like melanoma and non-small cell lung cancer where immunotherapy has been successful, thus providing a rationale to extrapolate immunotherapy to MCC [25]. Although data on the role of immunotherapy in the neoadjuvant setting is limited, the efficacy of pembrolizumab and avelumab in treatment-naïve patients, coupled with the greater responses observed with avelumab in patients with fewer lines of previous treatment, suggest a promising role for immunotherapy in that setting. Kaufman suggested that the immune system may be more functional in patients who had received fewer lines of therapy, thus accounting for greater responses to immunotherapy in this subset of patients [10]. As MCC is commonly localized to the head and neck areas, neoadjuvant treatment can potentially abrogate the need for potentially disfiguring surgery, as in our patient.

## Conclusion

Preclinical and clinical data thus far has shown a promising role for PD-1/PD-L1 inhibitors in advanced MCC and suggests a potential role in the neoadjuvant setting. As the incidence of MCC is increasing, clinical trials to further explore the efficacy and safety of immunotherapy in resectable MCC are needed.

## Declaration of Competing Interest

The authors have not received any funding for this study and declare no direct conflict of interest. Dr. Sukari serves on the advisory board for Eisai and a speaker for Merck and Eisai. He has received study funding from Eisai. Dr. Nagasaka serves on the advisory board for AstraZeneca and has received research support from Tempus. Dr. Abdallah has nothing to declare.

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## Ethics approval and consent to participate

Need for approval was waived by the Karmanos Protocol Review and Monitoring Committee. Consent for publication: Consent for treatment and publication was obtained from the patient himself.

## References

[1] Grabowski J, Saltzstein SL, Sadler GR, Tahir Z, Blair S. A comparison of Merkel cell carcinoma and melanoma: results from the California cancer registry. Clin Med Oncol 2008;2:327–33.
[2] Heath M, Jaimes N, Lemos B, Mostaghimi A, Wang LC, Penas PF, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. J Am Acad Dermatol 2008;58(3):375–81.
[3] Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science 2008;319(5866):1096–100.
[4] Wong SQ, Waldeck K, Vergara IA, Schroder J, Madore J, Wilmott JS, et al. UV-associated mutations underlie the etiology of MCV-negative Merkel cell carcinomas. Cancer Res 2015;75(24):5228–34.
[5] Harms KL, Healy MA, Nghiem P, Sober AJ, Johnson TM, Bichakjian CK, et al. Analysis of prognostic factors from 9387 Merkel cell carcinoma cases forms the basis for the new 8th edition AJCC staging system. Ann Surg Oncol 2016;23(11):3564–71.
[6] Iyer JG, Blom A, Doumani R, Lewis C, Tarabadkar ES, Anderson A, et al. Response rates and durability of chemotherapy among 62 patients with metastatic Merkel cell carcinoma. Cancer Med 2016;5(9):2294–301.
[7] Fitzgerald TL, Dennis S, Kachare SD, Vohra NA, Wong JH, Zervos EE. Dramatic increase in the incidence and mortality from Merkel cell Carcinoma in the United States. Am Surg 2015;81(8):802–6.
[8] Paulson KG, Park SY, Vandeven NA, Lachance K, Thomas H, Chapuis AG, et al. Merkel cell carcinoma: current US incidence and projected increases based on changing demographics. J Am Acad Dermatol 2018;78(3). pp. 457–63 e2.
[9] Bichakjian CK, Olencki T, Aasi SZ, Alam M, Andersen JS, Blitzblau R, et al. Cell Carcinoma, version 1.2018, NCCN clinical practice guidelines in oncology. J National Comprehens Cancer Netw: JNCCN 2018;16(6):742–74.
[10] Kaufman HL, Russell J, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, et al. Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: a multicentre, single-group, open-label, phase 2 trial. Lancet Oncol 2016;17(10):1374–85.
[11] D'Angelo SP, Russell J, Hassel J, Lebbé C, Chmielowski B, Rabinowits G, et al. 1227PAvelumab treatment in chemotherapy-naïve patients with distant metastatic Merkel cell carcinoma (mMCC). Ann Oncol 2017;28(suppl_5). mdx377.014-mdx377.014.
[12] Nghiem PT, Bhatia S, Lipson EJ, Kudchadkar RR, Miller NJ, Annamalai L, et al. PD-1 blockade with Pembrolizumab in advanced Merkel -Cell Carcinoma. N Engl J Med 2016;374(26):2542–52.
[13] Topalian SL, Bhatia S, Kudchadkar RR, Amin A, Sharfman WH, Lebbe C, et al. Nivolumab (Nivo) as neoadjuvant therapy in patients with resectable Merkel cell carcinoma (MCC) in CheckMate 358. J Clin Oncol 2018;36(15_suppl):9505.
[14] Nghiem P, Bhatia S, Lipson EJ, Sharfman WH, Kudchadkar RR, Friedlander PA, et al. Durable tumor regression and overall survival (OS) in patients with advanced Merkel cell carcinoma (aMCC) receiving pembrolizumab as first-line therapy. J Clin Oncol 2018;36(15_suppl):9506.
[15] Kaufman HL, Russell JS, Hamid O, Bhatia S, Terheyden P, D'Angelo SP, et al. Abstract CT079: Durable responses to avelumab (anti-PD-L1) in patients with Merkel cell carcinoma progressed after chemotherapy: 1-year efficacy update. Cancer Res 2017;77(13 Supplement). CT079-CT.
[16] Nghiem P, Bhatia S, Brohl AS, Hamid O, Mehnert JM, Terheyden P, et al. Two-year efficacy and safety update from JAVELIN Merkel 200 part A: a registrational study of avelumab in metastatic Merkel cell carcinoma progressed on chemotherapy. J Clin Oncol 2018;36(15_suppl):9507.
[17] D'Angelo SP, Russell J, Lebbé C, et al. Efficacy and safety of first-line avelumab treatment in patients with stage iv metastatic Merkel cell carcinoma: a preplanned interim analysis of a clinical trial. JAMA Oncol 2018;4(9):e180077.
[18] Paulson KG, Iyer JG, Blom A, Warton EM, Sokil M, Yelistratova L, et al. Systemic immune suppression predicts diminished Merkel cell carcinoma-specific survival independent of stage. J Invest Dermatol 2013;133(3):642–6.
[19] Paulson KG, Iyer JG, Simonson WT, Blom A, Thibodeau RM, Schmidt M, et al. CD8+ lymphocyte intratumoral infiltration as a stage-independent predictor of Merkel cell carcinoma survival: a population-based study. Am J Clin Pathol 2014;142(4):452–8.
[20] Muirhead R, Ritchie DM. Partial regression of Merkel cell carcinoma in response to withdrawal of azathioprine in an immunosuppression-induced case of metastatic Merkel cell carcinoma. Clin Oncol (R Coll Radiol) 2007;19(1):96.
[21] Wooff JC, Trites JR, Walsh NM, Bullock MJ. Complete spontaneous regression of metastatic Merkel cell carcinoma: a case report and review of the literature. Am J Dermatopathol 2010;32(6):614–7.
[22] Schadendorf D, Lebbe C, Zur Hausen A, Avril MF, Hariharan S, Bharmal M, et al. Merkel cell carcinoma: epidemiology, prognosis, therapy and unmet medical needs. Eur J Cancer 2017;71:53–69.
[23] Tetzlaff MT, Nagarajan P. Update on Merkel cell carcinoma. Head and Neck Pathol 2018;12(1):31–43.
[24] Schadendorf D, Nghiem P, Bhatia S, Hauschild A, Saiag P, Mahnke L, et al. Immune evasion mechanisms and immune checkpoint inhibition in advanced Merkel cell carcinoma. Oncoimmunology 2017;6(10):e1338237.
[25] Goh G, Walradt T, Markarov V, Blom A, Riaz N, Doumani R, et al. Mutational landscape of MCPyV-positive and MCPyV-negative Merkel cell carcinomas with implications for immunotherapy. Oncotarget 2016;7(3):3403–15.

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