AOMA 2024 Oral Clinical Case Presentation

Title: Advanced Merkel Cell Carcinoma in Setting of Pembrolizumab Therapy for Metastatic Squamous Cell Carcinoma

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ABSTRACT

Merkel cell carcinoma is a neuroendocrine tumor commonly found in patients of old age, immunosuppression, and extensive ultraviolet exposure. Characterized by its high recurrence, early metastasis, rapid growth, and poor prognosis, Merkel cell carcinoma is currently managed via definitive excision followed by radiation therapy or immunotherapy.[1-3] Pembrolizumab, a programmed cell death receptor 1 inhibiting monoclonal antibody, is an immunotherapy agent approved for treatment of Merkel cell carcinoma.[4] A rare adverse reaction termed hyperprogressive disease is a phenomenon in which a malignancy paradoxically experiences accelerated growth after immunotherapy initiation.[5-6] It is explained by two leading pathophysiological theories - adaptive immunity to immunotherapy or modified innate immunity, either of which foster pro-oncogenic environments.[7] Numerous case reports and studies explore hyperprogressive disease but fail to address application of this concept in different disease models such as newly arising tumors or cancer phenotype alteration.[8] We report an 86-year-old female patient receiving pembrolizumab treatment for metastatic squamous cell carcinoma who presented with a 3.5 x 3.5 x 2.0 cm Merkel cell carcinoma on her scalp, confirmed by histopathology. On her five-week follow-up post-resection, the patient presented with two new larger lesions of Merkel cell carcinoma around the same area of her scalp, the first measuring 8.0 x 6.0 x 4.0 cm and the second measuring 5.0 x 4.0 x 3.0 cm. The patient's paradoxical and aggressive development of Merkel cell carcinoma while receiving pembrolizumab for a different metastatic cancer is explained by the hyperprogressive disease model applied to a de novo malignancy and is the first of its kind reported in literature.

INTRODUCTION

Merkel cell carcinoma (MCC) is a neuroendocrine tumor that originates from a slow-acting mechanoreceptor in the stratum basale.[1] Patients of old age, immunosuppression, and extensive UV exposure are at increased risk of developing MCC, which is characterized by its high recurrence, early metastasis, rapid growth, and poor prognosis.[1-2] Tripling its incidence in the past 15 years, MCC has been of increasing dermatological concern and is currently managed via sentinel lymph node biopsy with definitive excision, followed by radiation therapy or immunotherapy.[1-3]

Initially implemented for treatment of refractory melanoma, pembrolizumab is FDA approved for the treatment of squamous cell carcinoma (SCC), MCC, and numerous advanced cancers.[4] Pembrolizumab is programmed cell death receptor 1 (PD-1) inhibiting IgG4 monoclonal antibody that prevents PD-1 induced T-cell inactivation by tumor cells.[5] Adverse reactions include skin reactions such as Stevens-Johnson syndrome and bullous pemphigoid, endocrinopathies, hepatotoxicity, nephrotoxicity, and allergic reactions.[4]

Among patients receiving immunotherapy, a rare phenomenon termed hyperprogressive disease (HPD) has been found to occur.[6] First documented in 2016, this poorly understood mechanism manifests as a malignancy paradoxically experiencing accelerated growth after immunotherapy initiation.[7] Numerous case reports and studies explore HPD but fail to address application of this concept in different disease models such as newly arising tumors or cancer phenotype alterations.[8]

We report a case of paradoxical MCC occurring in the setting of pembrolizumab therapy for metastatic SCC.

CASE REPORT

We report an 86-year-old female patient receiving pembrolizumab treatment for metastatic squamous cell carcinoma who presented with a painful, non-bleeding, non-pruritic, raised lesion on her head. The patient initially noticed her lesion two weeks prior to presentation, two weeks into her first immunotherapy session, and reported rapid growth of the mass.

The patient had a past medical history of over fifty squamous cell carcinomas of the skin status post multiple excisions and radiation treatments, essential thrombocythemia, chronic kidney disease, deep vein thrombosis, atrial fibrillation, hypertension, and leukemia. Concomitant medications included amlodipine, metoprolol, triamterene-hydrochlorothiazide, warfarin, anagrelide, ruxolitinib, and pembrolizumab. In addition, she had an extensive history of tanning bed use.

Local examination revealed a firm, non-mobile 3.5 x 3.5 x 2.0 cm erythematous papule with associated heme crusting and secondary impetiginization on the right posterior lateral vertex of the scalp (Figure 1, A). A partial resection of the mass was performed due to high clinical suspicion of Merkel cell carcinoma and was sent for histopathology and with referral to oncology for a PET scan.

Dermatopathology report revealed findings consistent with primary cutaneous neuroendocrine carcinoma, also known as Merkel cell carcinoma, extending to base and edge with lymph vascular and fatty invasion, classified as stage pT2. Microscopic description included sheet-like to trabecular proliferation of relatively uniform, small, round to oval cells with finely dispersed chromatin, numerous mitotic figures, and single-cell necrosis (Figure 2, A and B). The tumor cells had scant cytoplasm that is reactive in a punctate paranuclear pattern positive for cytokeratin, synaptophysin, and chromogranin, but negative for p63 (Figure 2, C and D).

PET scan findings revealed an intensely hypermetabolic exophytic lesion of the right vertex scalp, compatible with MCC, along with bilateral mild to moderately hypermetabolic cervical chain lymph nodes, highly suspicious for regional nodal metastases.

Upon follow-up 5 weeks later, the patient presented with two new, similar but larger lesions around the same area of her scalp, the first measuring 8.0 x 6.0 x 4.0 cm on the right posterior vertex and the second measuring 5.0 x 4.0 x 3.0 cm on the right posterior occipital scalp (Figure 1, B).

Immunotherapy was stopped and radiation therapy was initiated. Upon follow-up three months later, there was significant reduction in size of both tumors (Figure 3).

DISCUSSION

MCC is a cutaneous neuroendocrine tumor of aggressive nature with the highest non-melanoma skin cancer death rate.[9] Although pathogenesis is understood to be multifactorial, 80% of MCC cases are seropositive for Merkel cell polyomavirus (MCPyV), a virus that is believed to behave similarly to the human papilloma virus. MCC typically presents as a pink or violaceous papule, nodule, or plaque with rapid growth that is histologically variable.[10] It is essential to differentiate MCC from small cell carcinoma of the lung via immunohistochemistry, where MCC will reveal positive staining for cytokeratin 20 and negative staining for cytokeratin 7 and thyroid transcription factor 1.[11] MCC has poor prognosis with 5-year survival rates at 51% for localized disease, 35% for nodal involvement, and 14% for metastasis.[10] Factors of poor prognosis include negative MCPyV serology, positive p63 staining, and primary tumor size over 2 cm.[11,12]

The occurrence of MCC in a patient receiving pembrolizumab treatment presents a paradoxical scenario due to the immunotherapy being approved to treat the condition itself. With her advanced age, history of multiple malignancies, and personal history of UV exposure, the patient is already at a high risk for developing MCC. However, whether the cancer was developing prior to onset of immunotherapy and inadvertently but poorly controlled by it, or an HPD was manifesting, is unclear.

The pathophysiology of HPD is explained by either of two leading theories – adaptive immunity to immunotherapy or modified innate immunity. The first describes tumor cells' ability to evade PD-1 inhibition via upregulation of other T-cell inhibition mechanisms. Notably, the upregulation of T-cell immunoglobulin mucin-3 (TIM-3), an alternative immune checkpoint, has been observed in successful adaptive resistance and increased survival of tumor cells. Furthermore, TIM-3 blockade in mice has demonstrated clinical benefit.[13] PD-1 inhibition, beyond its effects on T-cells, alters innate immune system functioning. Major findings reveal that PD-1 blockade can impair the ability for natural killer cells to produce perforins and granzymes, promote interleukin-10 release from type 3 innate lymphoid cells, dendritic cells, and monocytes, and hinder antigen presentation, overall promoting a pro-oncotic

environment.[6,14] These mechanisms may be applicable to our patient's scenario, where pembrolizumab therapy may have induced HPD in a pre-existing MCC or fostered development of a new MCC.

CONCLUSION

This is a case of MCC occurring in the setting of pembrolizumab therapy for metastatic SCC. HPD, a poorly understood phenomenon that occurs in patients receiving immunotherapy has only been documented to occur while being treated for a pre-existing malignancy. The aggressive nature, rapid recurrence, and disease presentation of this patient's MCC allow us to attribute the rare, paradoxical presentation to a potential hyperprogressive disease model applied to a de novo malignancy.

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None

ABBREVIATIONS AND ACRONYMS

FDA – Food and drug administration

HPD – Hyperprogressive disease

IgG4 – Immunoglobulin G4

MCC – Merkel cell carcinoma

PD-1 – Programmed cell death receptor-1

PET – Positron emission tomography

SCC – Squamous cell carcinoma

TIM-3 – T-cell immunoglobulin mucin-3

UV – Ultraviolet

REFERENCES*

1. Albores-Saavedra, J., Batich, K., Chable-Montero, F., Sagy, N., Schwartz, A. M., & Henson, D. E. (2009). Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: A population based study. *Journal of Cutaneous Pathology, 37*(1), 20–27. https://doi.org/10.1111/j.1600-0560.2009.01370.x
2. Pulitzer, M. (2017). Merkel cell carcinoma. *Surgical Pathology Clinics, 10*(2), 399–408. https://doi.org/10.1016/j.path.2017.01.013
3. Gunaratne, D. A., Howle, J. R., & Veness, M. J. (2017). Definitive radiotherapy for merkel cell carcinoma confers clinically meaningful in-field locoregional control: A review and analysis of the literature. *Journal of the American Academy of Dermatology, 77*(1). https://doi.org/10.1016/j.jaad.2017.02.015
4. Castro, G. de, Kudaba, I., Wu, Y.-L., Lopes, G., Kowalski, D. M., Turna, H. Z., Caglevic, C., Zhang, L., Karaszewska, B., Laktionov, K. K., Srimuninnimit, V., Bondarenko, I., Kubota, K., Mukherjee, R., Lin, J., Souza, F., Mok, T. S., & Cho, B. C. (2021). 363 keynote-042 5-year survival update: Pembrolizumab versus chemotherapy in patients with previously untreated, PD-L1–positive, locally advanced or metastatic non–small-cell lung cancer. *Journal for ImmunoTherapy of Cancer, 9*(Suppl 2). https://doi.org/10.1136/jitc-2021-sitc2021.363
5. Pardoll, D. M. (2012). The blockade of immune checkpoints in cancer immunotherapy. *Nature Reviews Cancer, 12*(4), 252–264. https://doi.org/10.1038/nrc3239
6. Camelliti, S., Le Noci, V., Bianchi, F., Moscheni, C., Arnaboldi, F., Gagliano, N., Balsari, A., Garassino, M. C., Tagliabue, E., Sfondrini, L., & Sommariva, M. (2020). Mechanisms of hyperprogressive disease after immune checkpoint inhibitor therapy: What we (don't) know. *Journal of Experimental & Clinical Cancer Research, 39*(1). https://doi.org/10.1186/s13046-020-01721-9

7. Chubachi, S., Yasuda, H., Irie, H., Fukunaga, K., Naoki, K., Soejima, K., & Betsuyaku, T. (2016). A case of non-small cell lung cancer with possible “Disease flare” on nivolumab treatment. *Case Reports in Oncological Medicine, 2016,* 1–3. https://doi.org/10.1155/2016/1075641
8. Champiat, S., Dercle, L., Ammari, S., Massard, C., Hollebecque, A., Postel-Vinay, S., Chaput, N., Eggermont, A., Marabelle, A., Soria, J.-C., & Ferté, C. (2017). Hyperprogressive disease is a new pattern of progression in cancer patients treated by Anti-PD-1/PD-L1. *Clinical Cancer Research, 23*(8), 1920–1928. https://doi.org/10.1158/1078-0432.ccr-16-1741
9. Agelli, M., & Clegg, L. X. (2003). Epidemiology of primary Merkel cell carcinoma in the United States. *Journal of the American Academy of Dermatology, 49*(5), 832–841. https://doi.org/10.1016/s0190-9622(03)02108-x
10. Coggshall, K., Tello, T. L., North, J. P., & Yu, S. S. (2018). Merkel cell carcinoma: An update and Review. *Journal of the American Academy of Dermatology, 78*(3), 433–442. https://doi.org/10.1016/j.jaad.2017.12.001
11. Jaeger, T., Ring, J., & Andres, C. (2012). Histological, immunohistological, and clinical features of Merkel cell carcinoma in correlation to Merkel cell polyomavirus status. *Journal of Skin Cancer, 2012,* 1–5. https://doi.org/10.1155/2012/983421
12. Stokes, J. B., Graw, K. S., Dengel, L. T., Swenson, B. R., Bauer, T. W., Slingluff, C. L., & Ledesma, E. J. (2009). Patients with Merkel cell carcinoma tumors ≤1.0 cm in diameter are unlikely to harbor regional lymph node metastasis. *Journal of Clinical Oncology, 27*(23), 3772–3777. https://doi.org/10.1200/jco.2008.20.8272
13. Koyama, S., Akbay, E. A., Li, Y. Y., Herter-Sprie, G. S., Buczkowski, K. A., Richards, W. G., Gandhi, L., Redig, A. J., Rodig, S. J., Asahina, H., Jones, R. E., Kulkarni, M. M., Kuraguchi, M., Palakurthi, S., Fecci, P. E., Johnson, B. E., Janne, P. A., Engelman, J. A., Gangadharan, S. P., Costa, D. B., Freeman, G. J., Bueno, R., Hodi, F. S., Dranoff, G., Wong, K. K., & Hammerman, P. S. (2016). Adaptive resistance to therapeutic PD-1 blockade is associated with upregulation of

alternative immune checkpoints. *Nature Communications, 7*(1). https://doi.org/10.1038/ncomms10501

14. Solaymani-Mohammadi, S., Lakhdari, O., Minev, I., Shenouda, S., Frey, B. F., Billeskov, R., Singer, S. M., Berzofsky, J. A., Eckmann, L., & Kagnoff, M. F. (2015). Lack of the programmed death-1 receptor renders host susceptible to enteric microbial infection through impairing the production of the Mucosal Natural Killer Cell effector molecules. *Journal of Leukocyte Biology, 99*(3), 475–482. https://doi.org/10.1189/jlb.4a0115-003rr

* Osteopathic literature on Merkel cell carcinoma is not available

FIGURE LEGEND

Figure 1 “Merkel cell carcinoma of scalp. A, Solitary lesion at initial presentation. B, Two new lesions on five-week follow-up”

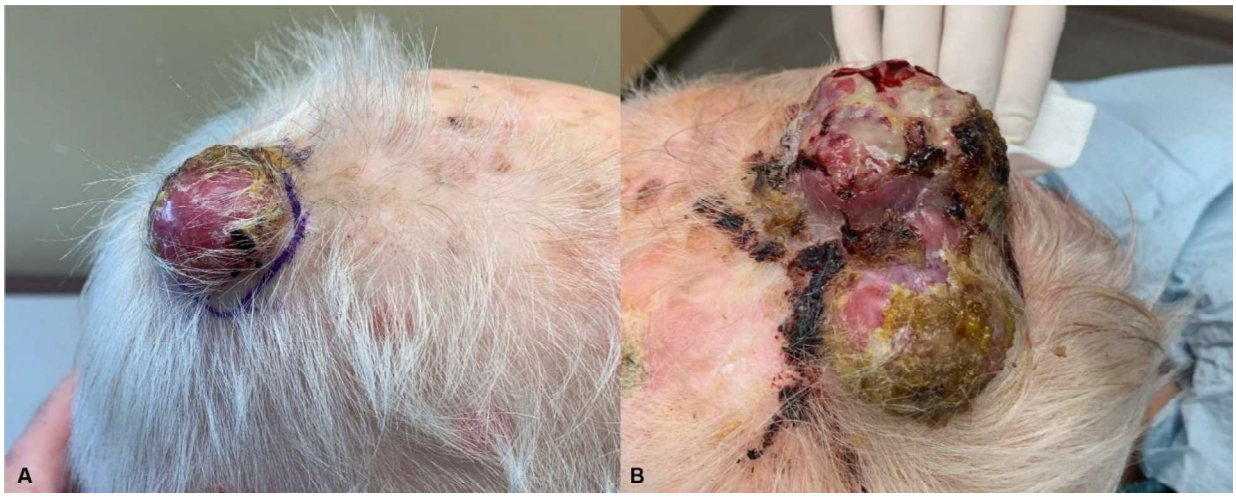

Figure 2 “Histopathology of the Merkel cell carcinoma. A, Sheet-like to trabecular proliferation of relatively uniform, small, round to oval cells (Hematoxylin-eosin stain; original magnification x 10). B, Neoplastic cells will finely dispersed chromatin, numerous mitotic figures, and single-cell necrosis (Hematoxylin-eosin stain; original magnification x 40). C, Punctate paranuclear pattern positive for cytokeratin (Original magnification x 10). D, Immunohistochemistry with synaptophysin (Original magnification x 10).”

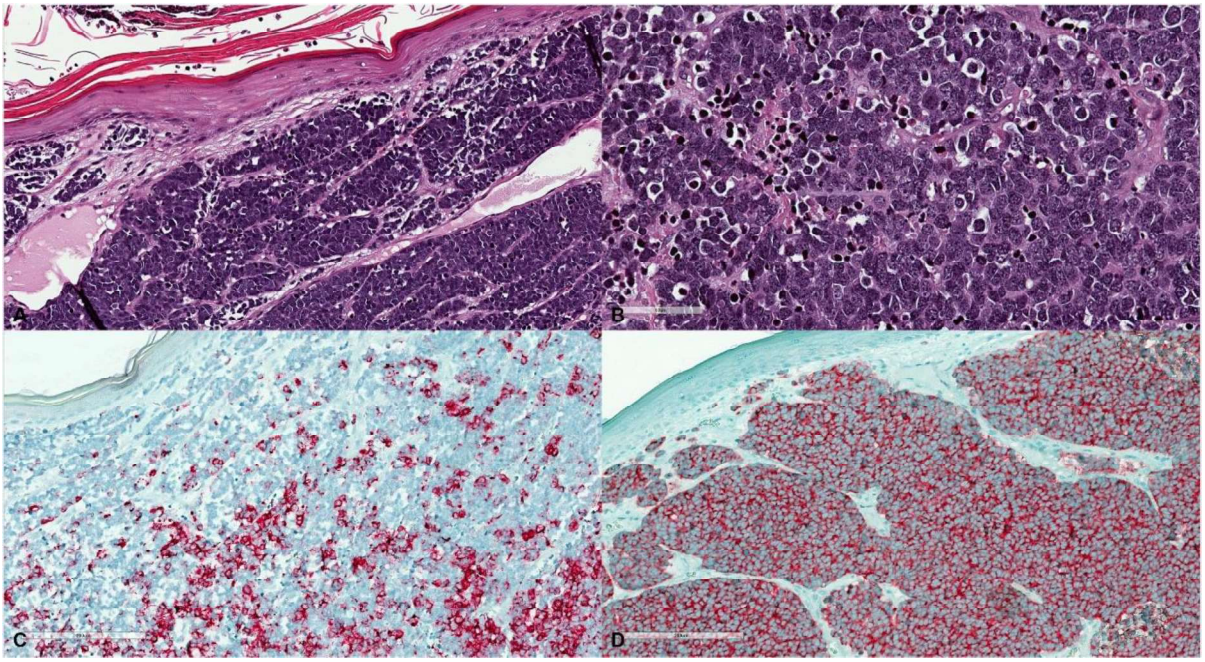

Figure 3 “Three-month follow-up after radiation therapy of Merkel cell carcinoma and discontinuation of pembrolizumab.”