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Merkel Cell Polyomavirus-Negative Merkel Cell Carcinoma Presenting in the Parotid Gland: Precise Diagnosis and Complete Pathological Response to Nivolumab

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Abstract

Background/Aim: Merkel cell carcinoma (MCC) is a rare and aggressive cutaneous neuroendocrine carcinoma that may present diagnostic challenges, particularly in Merkel cell polyomavirus (MCPyV)-negative cases. Distinguishing MCC from other high-grade neuroendocrine carcinomas is critical because treatment strategies differ.

Case report: We report a case of a 77-year-old Caucasian male with a history of multiple non-melanoma skin cancers who presented with rapidly enlarging left parotid and cervical lymph node masses with suspected osseous metastasis to the fourth cervical vertebra (C4). Fine needle aspiration of the parotid mass demonstrated high-grade neuroendocrine carcinoma, positive for synaptophysin, focally and weakly positive for cytokeratin 20 (CK20), and negative for thyroid transcription factor 1 (TTF-1) and Merkel cell polyomavirus (MCPyV) immunoreactivity. Initial molecular classification favored small cell carcinoma. However, additional mutational signature analysis demonstrated an ultraviolet (UV) mutational profile consistent with cutaneous origin, supporting MCPyV-negative Merkel cell carcinoma. The diagnosis was revised following multidisciplinary review, and planned treatment was changed from carboplatin-etoposide chemotherapy to three months of nivolumab, a programmed death-1 (PD-1) inhibitor. Surgical resection of the parotid gland demonstrated complete pathologic response with no residual viable carcinoma identified. At the two-year follow-up, the patient was doing well with no MCC recurrence or metastasis identified.

Conclusion: This case highlights the diagnostic difficulty of MCPyV-negative MCC presenting in an extracutaneous location and mimicking small cell carcinoma. In diagnostically challenging MCCs, molecular profiling and UV mutational signature analysis may play a key role in establishing correct diagnosis and treatment.

Keywords: Merkel cell polyomavirus (MCPyV), Merkel cell carcinoma, small cell carcinoma, immunohistochemistry, next-generation sequencing (NGS), UV mutational signature, programmed death-1 (PD-1) inhibitor immunotherapy.

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Introduction

Merkel cell carcinoma (MCC) is a rare and highly aggressive cutaneous neuroendocrine carcinoma predominantly affecting elderly patients with fair skin. MCC often presents as a rapidly growing nodule and is associated with a high risk of regional lymph node involvement and distant metastasis, contributing to its poor prognosis (1).

MCC pathogenesis is broadly divided into two major categories. Most cases are associated with Merkel cell polyomavirus (MCPyV). The other main category comprises MCPyV-negative tumors, which are associated with ultraviolet (UV)-induced mutagenesis and chronic sun exposure (2). Advances in treatment, particularly the introduction of anti-programmed death-1 (PD-1) immune checkpoint inhibitors, have significantly improved outcomes in MCC (3).

MCC has a strong tendency for regional lymph node and distant metastasis, and in some cases may present without an identifiable cutaneous primary lesion. Extracutaneous presentation, including involvement of intraparotid lymph nodes or cervical lymph nodes, can complicate diagnosis and may mimic other high-grade neuroendocrine carcinomas such as small cell carcinoma. Merkel cell carcinoma of unknown primary has been described in lymph nodes and the parotid gland (4), and nodal MCC has been reported to show a lower association with MCPyV compared with cutaneous cases, further increasing diagnostic uncertainty (5). In such clinically challenging scenarios, integration of histopathology, immunohistochemistry, and molecular profiling is essential for accurate diagnosis and optimal management. In our case, molecular evaluation, including mutational signature analysis, was key in establishing the correct diagnosis and guiding treatment, ultimately resulting in a favorable outcome.

To the best of our knowledge, this represents the first reported case of MCPyV-negative Merkel cell carcinoma initially diagnosed as small cell carcinoma in which ultraviolet mutational signature analysis led to revision of the diagnosis and a change in treatment strategy. The patient in the present case had an excellent treatment outcome at the two-year follow-up. The diagnostic challenges, treatment, and prognosis of this rare presentation are discussed. Written informed consent for clinical education/research including publication was obtained.

Case report

A 77-year-old white male with a history of multiple non-melanoma skin cancers presented with a progressively enlarging left neck mass that had been present for approximately two months. Review of prior pathology reports from 2006 to 2023 demonstrated multiple basal cell carcinomas and one compound melanocytic nevus with mild atypia in 2008. The patient reported that the neck mass had appeared approximately two months prior to presentation and that one to two additional adjacent nodules developed shortly thereafter. Antibiotic therapy was attempted without improvement.

Computed tomography (CT) demonstrated a left parotid mass (2.5 cm), an enlarged level II lymph node, as well as a lytic lesion involving the left transverse process of the fourth cervical vertebra (C4) suspicious for metastatic disease (Figure 1A). Positron emission tomography/computed tomography (PET/CT) of the neck demonstrated superficial and lower pole hypermetabolic masses within the left parotid gland measuring 2.5 cm and 1.3 cm in the greatest dimension, respectively, which were interpreted as possible intraparotid lymph nodes *versus* primary parotid lesions. In addition, a large fluorodeoxyglucose-avid left level II lymph node measuring 2.2×2.0×1.6 cm was identified (Figure 1B). Magnetic resonance imaging (MRI) confirmed multiple enhancing lesions in the superficial lobe of the left parotid gland and enlarged cervical lymph nodes suspicious for metastases.

Fine needle aspiration (FNA) of the left parotid lesion was subsequently performed. Cytologic smears and cell block sections demonstrated sheets of monotonous malignant cells with small, round, hyperchromatic nuclei, scant cytoplasm, and frequent mitotic figures (Figure 1C and D). Many scattered lymphocytes were present in the background, and no benign parotid tissue was identified.

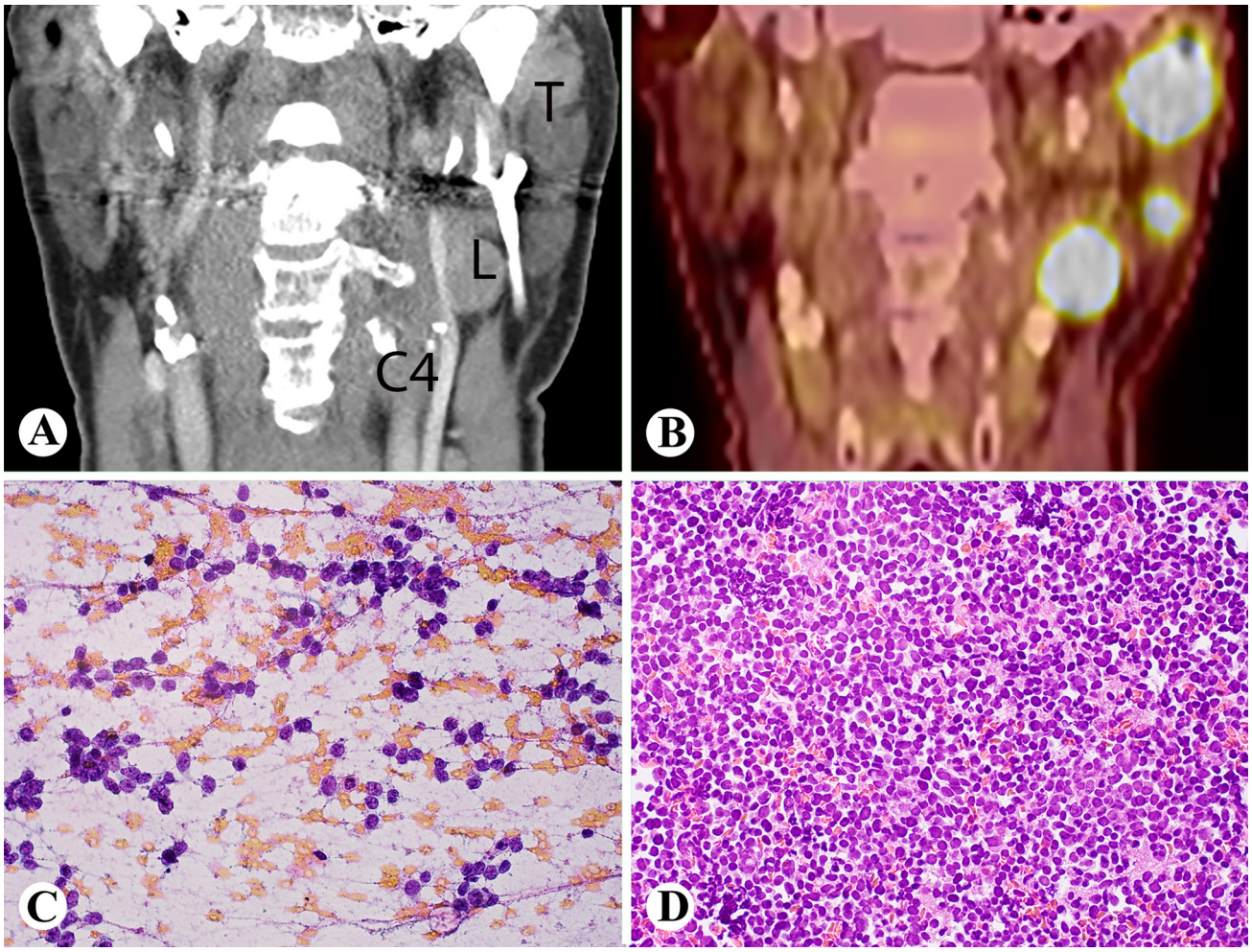


Figure 1. *Parotid gland Merkel cell carcinoma with metastasis to cervical vertebra 4 (C4) and neck lymph node. (A) Computed tomography (CT) scan (coronal) showing left parotid mass (T), enlarged level II neck lymph node (L) and C4 lytic lesion radiologically suspicious for osseous metastasis. (B) Positron emission tomography (PET)/CT showing left superficial parotid gland mass (2.5 cm, SUVmax 23.7) and lower pole nodule (1.3 cm, SUVmax 18.8) and left neck level II lymph node (2.2 cm, SUVmax 24.1). (C-D) Fine needle aspiration showing neuroendocrine carcinoma cells with a high nuclear-to-cytoplasmic (N/C) ratio and scant cytoplasm. C: Papanicolaou stain; D: cell block H&E stain; C-D: magnification ×400.*

Immunohistochemical studies showed tumor cells positive for synaptophysin (Figure 2A), chromogranin, cytokeratin CAM5.2 in a perinuclear dot-like pattern, focally and weakly positive for cytokeratin 20 (CK20) (Figure 2B), negative for thyroid transcription factor 1 (TTF-1), p63, and lymphocyte markers. Ki-67 proliferation index was approximately 30-40% (Figure 2C left), and p53 showed diffuse aberrant nuclear expression (Figure 2C right). Immunohistochemical staining for MCPyV, performed at Mayo Clinic Laboratories, was negative (Figure 2D). Based on morphology and immunophenotype, the findings were interpreted as high-grade neuroendocrine carcinoma, with a differential diagnosis including extrapulmonary small cell carcinoma and Merkel cell carcinoma. During multidisciplinary tumor board review, the morphology suggested the possibility of MCPyV-negative Merkel cell carcinoma of possible cutaneous origin.

Comprehensive genomic profiling (Caris Life Sciences, Phoenix, AZ, USA) was obtained to further characterize the tumor (6). Molecular analysis initially favored a poorly

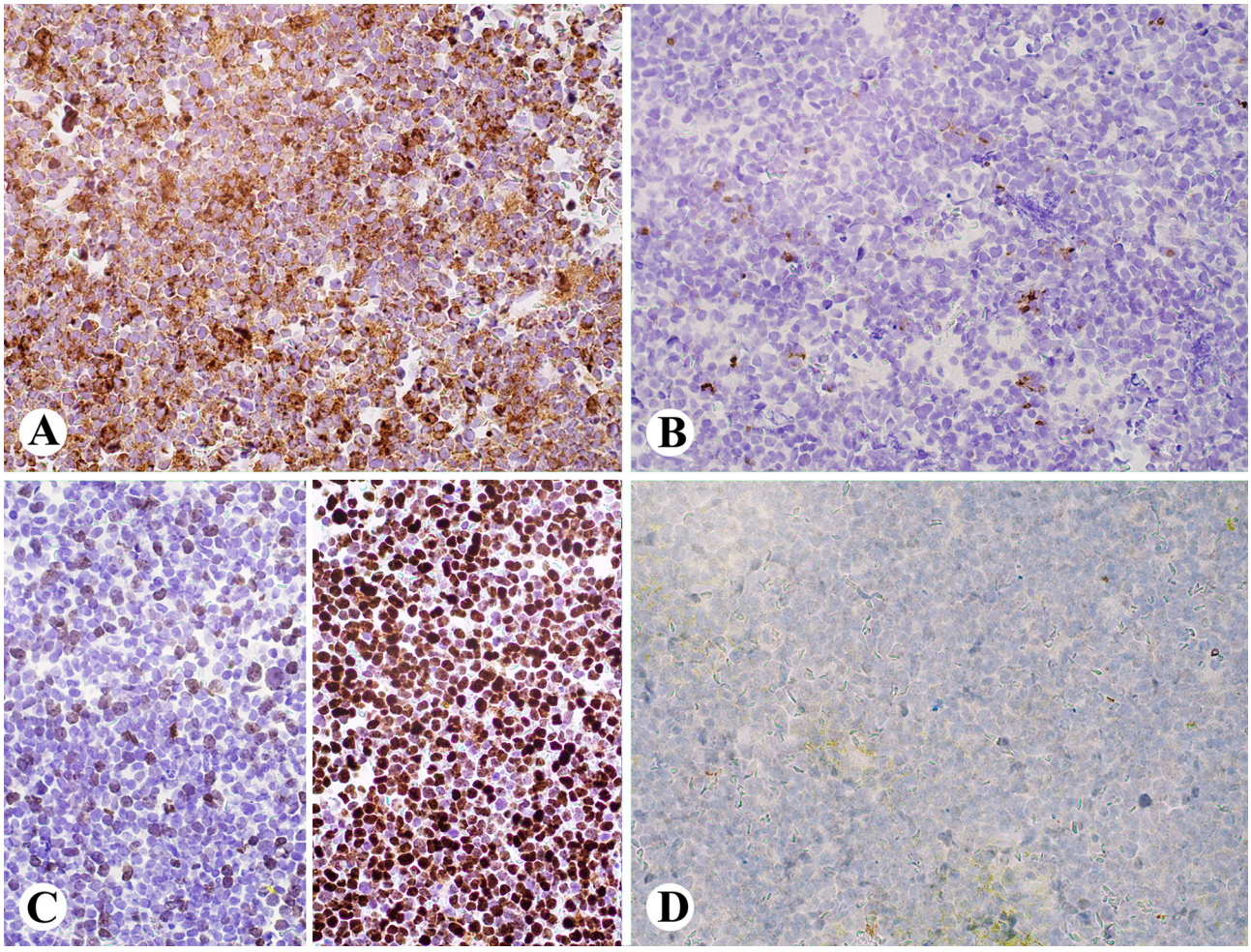


Figure 2. *Immunohistochemistry of the virus-negative Merkel cell carcinoma. The tumor cells are positive for synaptophysin (A) and focally positive for CK20 (B) with a Ki-67 labeling index of approximately 30-40% (C left), positive for p53 (C right), and negative for Merkel cell polyomavirus (MCPyV) (D). A-D: magnification ×400.*

differentiated neuroendocrine carcinoma, suggesting extrapulmonary small cell carcinoma as the most likely diagnosis. However, additional mutational signature analysis demonstrated a UV mutation pattern including pathogenic mutations of TP53, notch receptor 1 (NOTCH1), f-box and WD repeat-containing protein 7 (FBXW7), and lysine methyltransferase 2C (KMT2C), and a high tumor mutation burden (TMB, 33 mut/Mb) consistent with UV-associated cutaneous origin, although other alterations of breast cancer type 1 (BRCA1), tumor necrosis factor receptor superfamily member 14 (TNFRSF14), ERCC excision repair 6 (ERCC6) and neurofibromatosis type 1 (NF1) identified. The UV mutational signature and the presence of prominent tumor-infiltrating lymphocytes were characteristic of MCPyV-negative Merkel cell carcinoma.

Based on the initial interpretation of small cell carcinoma, treatment with reduced-dose carboplatin (area under the curve=4) and etoposide (80 mg/m^2) was planned. However, after review incorporating molecular findings, the diagnosis was revised to metastatic Merkel cell carcinoma, and treatment was changed to nivolumab, a programmed death-1 (PD-1) inhibitor.

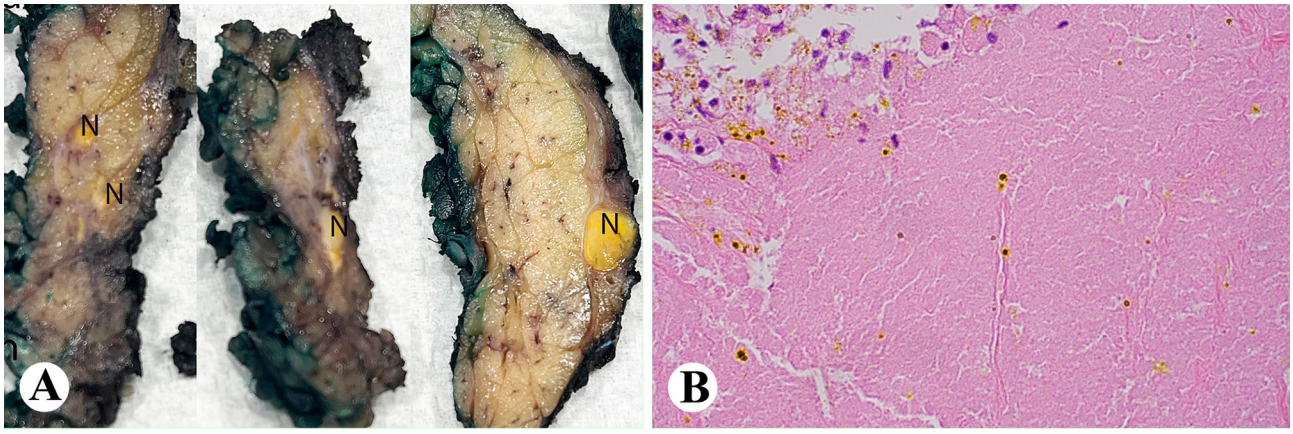


Figure 3. *Pathologic findings following nivolumab treatment. (A) Gross appearance of the serially sectioned left total parotidectomy specimen showing multiple necrotic nodules (N), which were entirely submitted for histologic examination. (B) Histologic examination of the treated nodules showing extensive tumor necrosis and fibrosis, with no residual viable carcinoma identified (H&E stain, magnification ×400).*

Following nivolumab immunotherapy for 3 months, the C4 lesion was no longer detectable on follow-up imaging, and the patient underwent left total parotidectomy with neck dissection. Gross examination of the parotid gland demonstrated multiple necrotic nodules, which were entirely submitted for histologic evaluation (Figure 3A). Microscopic examination showed tumor necrosis and fibrosis without residual viable carcinoma identified (Figure 3B). Immunohistochemical stains for synaptophysin and CAM5.2 were negative in the treated nodules. A total of 38 lymph nodes were examined, all negative for viable tumor. The histologic features were suggestive of complete treatment response to nivolumab. The final pathologic stage was ypT0N0M0, consistent with complete pathologic response after immunotherapy. At the two-year follow-up, the patient was doing well except for chronic neck pain. No MCC recurrence or metastasis was identified. Most recently, because of an elevated serum prostate-specific antigen level, the patient was diagnosed with prostate adenocarcinoma, and he subsequently underwent non-surgical treatment.

Discussion

Histologically, MCC is composed of small round blue cells with scant cytoplasm, finely granular chromatin, and frequent mitotic figures, features that significantly overlap with those of other high-grade neuroendocrine carcinomas, particularly small cell carcinoma. As a result, distinguishing MCC from small cell carcinoma can be challenging, especially when tumors present in lymph nodes or salivary glands without an identifiable cutaneous primary lesion as in the present case (7).

Immunohistochemistry plays an important role in differentiating MCC from other neuroendocrine cancers (8). However, immunophenotypic variability can occur, particularly in MCPyV-negative tumors, which may demonstrate focal or weak CK20 expression and atypical staining patterns (9). In such cases, reliance on immunohistochemistry alone may be insufficient to definitively distinguish MCC from small cell carcinoma.

MCC is divided into two major categories: MCPyV-associated and MCPyV-negative tumors. Approximately 80% of MCC cases are associated with clonal integration of MCPyV, whereas the remaining tumors are virus-negative and arise through UV-induced mutagenesis (10). MCPyV-negative MCCs typically exhibit a high tumor mutational burden with a characteristic UV signature, reflecting cumulative sun exposure. Importantly, nodal MCC has been reported to have a lower association with MCPyV compared with cutaneous MCC, which may further obscure the diagnosis in virus-negative cases (11). In this

setting, MCC may closely mimic metastatic small cell carcinoma, particularly when presenting in the parotid gland or lymph nodes.

Molecular profiling may provide information to determine tumor origin. Mutational signature analysis has emerged as a useful tool for distinguishing UV-driven cutaneous malignancies from other neuroendocrine carcinomas (12). In this case, initial molecular classification suggested poorly differentiated neuroendocrine carcinoma with features favoring small cell carcinoma. However, identification of a UV mutational signature supported a cutaneous origin, leading to revision of the diagnosis to MCPyV-negative MCC.

Accurate distinction between MCC and small cell carcinoma has significant therapeutic implications. Small cell carcinoma is typically treated with platinum-based chemotherapy regimens such as carboplatin and etoposide, whereas advanced MCC is preferentially treated with immune checkpoint inhibitors targeting the PD-1/programmed death-ligand 1 (PD-L1) pathway (3, 13). Recent studies regarding checkpoint inhibition in MCC have demonstrated good responses, leading to its adoption as first-line therapy in current clinical guidelines (14). Furthermore, MCPyV-negative MCCs with high tumor mutational burden may be particularly responsive to immunotherapy due to increased neoantigen load (12). In this case, revision of the diagnosis resulted in a change from cytotoxic chemotherapy to nivolumab, leading to a complete response (ypT0 N0 M0).

This report describes a single patient and cannot establish the general diagnostic or therapeutic applicability of UV mutational signature analysis or nivolumab in similar cases. In addition, the presumed C4 metastasis was based on imaging findings and treatment response rather than histological confirmation, and no cutaneous primary tumor was identified. Thus, although the molecular UV signature strongly supported a cutaneous origin and MCPyV-negative Merkel cell carcinoma, the precise primary site cannot be definitively established. Larger series with standardized molecular characterization and longer follow-up are needed to determine the diagnostic and therapeutic implications of this approach.

This case illustrates the diagnostic challenges associated with MCPyV-negative Merkel cell carcinoma presenting in an extracutaneous location and mimicking small cell carcinoma. In such cases, immunohistochemistry may be inconclusive, and molecular profiling, including mutational signature analysis, may be necessary to establish the correct diagnosis and guide appropriate treatment.

Conflicts of Interest

The Authors declare that they have no conflicts of interest regarding this case report.

Authors' Contributions

AZL wrote the article; DIC, SMP, and TRO conducted the patient management including biopsy, surgery and clinical follow-up; JL made the diagnosis, collected and analyzed the data, edited and finalized the article.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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