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Cytokeratin 20 negative nodal Merkel cell carcinoma with regressed primary: a potential pitfall in interpretation of nodal metastasis

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Abstract

Merkel cell carcinoma (MCC) is a rare, highly aggressive cutaneous neuroendocrine carcinoma that affects sun-damaged skin. Histologically, the tumor consists of round cells with fine chromatin positive for cytokeratin 20 in ~90% of cases. Rare cases of MCC can regress spontaneously and present as nodal metastasis. Nodal MCC of unknown primary can cause a potential pitfall as they can be misinterpreted as other neuroendocrine carcinomas such as small cell carcinoma. We report a case of nodal MCC with an atypical immunohistochemistry pattern presented as bilateral axillary lymphadenopathy in a 90-year-old man with a remote history of a skin lesion that healed spontaneously leaving a scar.

Keywords: CK-20, cytokeratin 20, Merkel cell carcinoma, neuroendocrine, nodal metastasis, regression, TTF1

Introduction

Merkel cell carcinoma (MCC) is the only primary neuroendocrine carcinoma of the skin (also known as trabecular carcinoma and Toker tumor), [1]. It is a rare highly aggressive skin cancer that affects elderly Caucasian individuals. In the United States, the estimated annual incidence of MCC is 0.23 per 100,000 in the Caucasian population compared to 0.01 per 100,000 in the African American population [2]. The median age at diagnosis is 75 years of age

with a slight male predilection [3]. Ultraviolet radiation exposure and genomic integration of the Merkel cell polyomavirus (MCPyV) are the two main identified etiological factors for MCC. Merkel cell polyomavirus is observed in about 80% of Merkel cell carcinoma cases and is associated with mutations of the viral sequence that lead to truncation of the large T antigen (LTA_g), [4].

Merkel cell carcinoma shows a propensity for sun-damaged skin with the head and neck (50%) and the extremities (40%) being the most common sites affected. It presents as a firm painless growing nodule or plaque. The overlying skin may be erythematous, violaceous, or less commonly ulcerated [5]. Complete spontaneous regression of MCC rarely occurs. It was first described by O'Rourke et. al in 1986 [6], with around 60 additional cases reported since then [7–12]. Spontaneous regression could explain the reported cases of MCC involving lymph nodes without a primary skin tumor [13–17]. Nodal MCC of unknown primary (NMCUP) can be misinterpreted on histological examination as metastasis from other neuroendocrine carcinomas such as small cell carcinoma. The distinction between these entities, although challenging, is crucial for proper management. Moreover, studies have suggested that primary neuroendocrine carcinomas can originate in lymph nodes [18,19].

Merkel cell carcinoma commonly metastasizes to regional lymph nodes (55%) and to distal organs (35%), particularly the liver, bone, lung, and skin [5].



Figure 1. A) Rapidly growing tumor on the mid back, appears as exophytic erythematous to violaceous nodule. **B)** Spontaneous regression of the tumor.

The five-year survival for distant disease is particularly poor at 25% compared to 59% for regional and 75% for localized disease. The standard therapy for MCC is usually wide local excision combined with adjuvant radiotherapy. Sentinel lymph node mapping may improve regional control of the disease and relapse-free survival [5]. The value of adjuvant chemotherapy and immunotherapy remains to be determined and is currently only used for the palliative treatment of metastatic MCC [20].

Case Synopsis

A 92-year-old man presented with a left axillary mass that appeared one month prior to presentation. In addition, he had a history of a skin lesions on his mid back that came up about a year ago (**Figure 1A**). The



Figure 2. A) Chest computed tomography demonstrating bilateral enlarged axillary lymph nodes. **B)** Positron emission tomography scan shows bulky markedly hypermetabolic bilateral axillary lymphadenopathy. The largest left axillary lymph node demonstrates marked peripheral hypermetabolism with central photopenia reflecting necrosis.

patient did not seek any medical attention and the lesion resolved spontaneously leaving a scar (**Figure 1B**). A computed tomography scan of the chest and a whole-body positron emission tomography scan showed multiple enlarged bilateral axillary lymph nodes, the largest on the left side (6.0cm), and a right posterior chest wall subcutaneous mass (2.1cm), (**Figure 2**). A biopsy from the left axillary mass showed relatively monotonous tumor cells with foci of necrosis and plasma cells in a background of T and B lymphocytes with T lymphocyte predominance (**Figure 3A**). The tumor cells were strongly positive for pankeratin, synaptophysin, chromogranin, and CD56. Few tumor cells were positive for cytokeratin (CK) 20 (**Figure 3B**). The tumor cells were negative for CK7 and focally weakly positive for thyroid transcription factor one TTF1 (**Figure 3C, D**). Neurofilament protein was negative. Polyoma virus immunostaining was performed, although it was difficult to read due to prominent background staining, the tumor cells appeared to be essentially negative for the polyoma virus immunostaining. The atypical immunostaining pattern of the tumor cells made differentiating between metastatic small cell

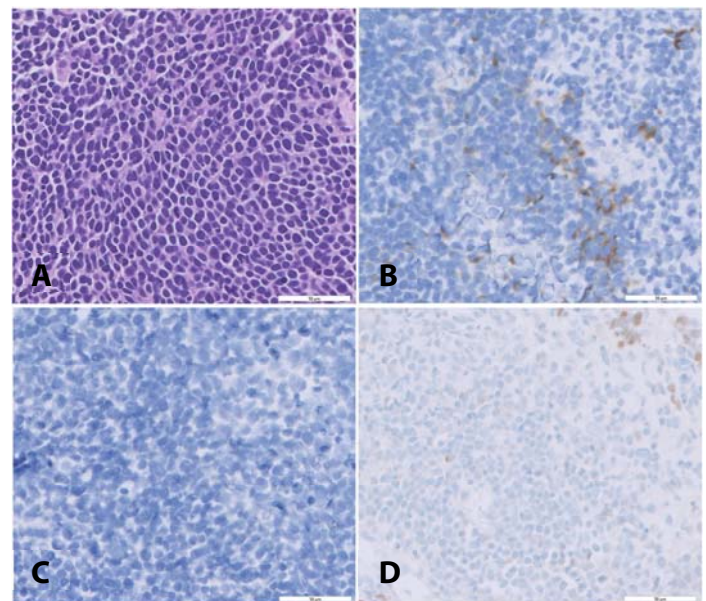


Figure 3. A) H&E histopathology showing large blue-cell tumor cells scant cytoplasm, stippled chromatin, focal nuclear molding and frequent mitosis. **B)** Only scattered tumor cells are immunoreactive for CK20 in a paranuclear dot pattern; the majority of the tumor cells are CK-20 negative. **C)** The tumor cells are negative for CK7. **D)** Weak expression TTF1 in few tumor cells. Scale bars=50µm.

carcinoma and metastatic MCC particularly challenging. However, the absence of dominant lung lesions or mediastinal lymphadenopathy and the history of a skin lesion raise the possibility of metastatic MCC. The patient declined further evaluation or biopsy from the skin lesion. Systemic treatment with carboplatin/etoposide was recommended which would cover both small cell and MCC; however, the patient elected against. The patient was transitioned into hospice care, where he died of disease three months following the initial diagnosis.

Case Discussion

Merkel cell carcinoma is an extremely aggressive skin tumor with mortality rate of around 25%. With an estimated 400 annual cases in the U.S., it is a rare malignancy. In 10% of cases, MCC presents as lymph node metastasis without a known primary cutaneous tumor. However, whether NMCUP constitutes an intranodal primitive neoplasia or a nodal metastasis from an occult or totally regressive skin MCC is still unknown. Distinguishing nodal MCC from metastatic other neuroendocrine carcinoma can be incredibly challenging especially when the immunohistochemistry staining is not distinctive.

Typically, CK20 positivity and negativity for TTF1 are used to distinguish Merkel cell carcinoma from other neuroendocrine carcinomas, especially bronchial small cell carcinoma [21]. In addition, MCC was found to express neuron-specific enolase (80%), neurofilament protein (50%), special AT-rich sequence-binding protein two [SATB2], and CD99 (19%). Cytokeratin 7, and MASH-1, are typically negative in MCC whereas positive in neuroendocrine carcinomas of bronchial origin [5,21]. However, variants of MCC can lack CK20 expression (10%) or show focal positivity for TTF1 [22,23]. Cytokeratin 20-negative MCC tends to lose expression of markers MCC-markers as neurofilament protein and STAB2 [21]. Moreover, MCPyV is less common in CK20-negative MCC, MCPyV has been reported to be negative in 77% of CK20-negative MCC cases which suggests non-viral oncogenesis of CK20 negative cases [24]. Detection of MCPyV using immunohistochemistry and molecular procedures

has been suggested for the diagnosis of Merkel cell carcinoma. However, the reported rates of MCPyV positivity were variable and demonstrated geographical differences [1,25].

Spontaneously regressed MCC is rare and has been estimated to occur in about 0.0013% of MCC cases. In previous studies, biopsies from regressed lesions demonstrated infiltration by T lymphocytes and macrophages with few cases showing fibrosis [26]. In our case, the patient declined further evaluation including biopsy of the regressed skin lesion.

Previous studies described NMCUPs to be more common in older individuals (>70 years of age), [27], with cervical, inguinal nodes, and axillary lymph nodes being the most common sites [28]. Microscopically NMCUP were of high-grade small cells with hyperchromatic nuclei and numerous mitoses [27,28], with increased inflammatory infiltrate with CD8-positive T lymphocytes [17]. By immunohistochemistry, almost all of the reported NMCUPs were positive for CK20 and ≥ 1 neuroendocrine marker (e.g., synaptophysin and chromogranin A), and negative for TTF1 and CK7 [27,28]. Nodal MCC of unknown primaries were reported to have a significantly lower association with MCPyV than the cutaneous MCCs [29].

Although there are still no standardized treatments for patients with metastatic MCC, therapeutic options are advancing. Recent clinical trials evaluating immune checkpoint inhibitors as avelumab (anti-PDL1) and pembrolizumab (anti-PD1) have shown an effective treatment option for such patients [30,31]. Chemotherapy has always been used to treat advanced disease; however, the associated benefit on overall survival is still unclear [32]. In the current case, given the bulk of the disease and the atypical immunophenotype which hindered the complete exclusion of metastatic small cell carcinoma, chemotherapy was preferred over immunotherapy, nevertheless, the patient ultimately declined all treatment.

Conclusion

Nodal MCC of unknown primary is a rare presentation of MCC and can pose a diagnostic

dilemma as it can be confused with more common metastatic neuroendocrine carcinomas as small cell lung cancer. Cases can exhibit atypical immunostaining pattern and can be either MCPyV-positive or -negative. Nodal MCC of unknown primaries should be considered in the differential of all cases of nodal metastasis with neuroendocrine features, particularly when deep carcinomas are excluded by imaging. Initial immunostains should include pan-CK, CK7, CK20, TTF1, chromogranin A, synaptophysin, and S100 to rule out a metastatic neuroendocrine carcinoma or melanoma. However,

one should keep in mind that about 10% of MCC can show atypical immunostaining pattern and therefore the negativity for CK20 should not exclude the diagnosis of metastatic MCC if clinically suspected. Careful review of patient history and proper clinical judgment are necessary to eliminate the possibility NMCUP.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Elder DE, Massi D, Scolyer RA. WHO Classification of Skin Tumours. vol. 11. 4th ed. WHO (World Health Organization); 2018.
2. Joshi AS, Nayak NS, Boone J. Merkel Cell Tumors of the Head and Neck: Overview, Pathophysiology and Etiology, Clinical Features. 2021. <https://emedicine.medscape.com/article/853565-overview#a4>. Accessed on October 28, 2021.
3. Albores-Saavedra J, Batich K, Chable-Montero F, et al. Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: a population based study. *J Cutan Pathol*. 2010;37:20–7. [PMID: 19638070].
4. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science*. 2008;319:1096–100. [PMID: 18202256].
5. Calonje E, Brenn T, Lazar AJ, MacKee PH, Billings SD (eds). McKee's pathology of the skin: with clinical correlations. Fifth edition. Elsevier; 2020.
6. O'Rourke MG, Bell JR. Merkel cell tumor with spontaneous regression. *J Dermatol Surg Oncol*. 1986;12:994–6, 1000. [PMID: 3745626].
7. Cirillo F. Spontaneous Regression of Primitive Merkel Cell Carcinoma. *Rare Tumors*. 2015;7:5961. [PMID: 26788270].
8. Terui H, Fujimura T, Kakizaki A, Furudate S, Aiba S. Merkel Cell Carcinoma with Spontaneous Regression: A Case Report and Immunohistochemical Study. *Case Rep Dermatol*. 2016;8:52–8. [PMID: 27293394].
9. Marcoval J, Valentí-Medina F, Penín RM, Bermejo J. Complete Spontaneous Regression of the Primary Tumor in Merkel Cell Carcinoma. *Actas Dermosifiliogr*. 2018;109:752–4. [PMID: 29631722].
10. Brownstein S, Mehta S, Nijhawan N, et al. Regression of Sebaceous Carcinoma of the Eyelid after a Small Incisional Biopsy: Report of Two Cases. *Ocul Oncol Pathol*. 2019;5:252–7. [PMID: 31367586].
11. Bystricky B, Kohutek F, Miklatkova Z, et al. Spontaneous Regression of Merkel Cell Carcinoma: Case Report. *Int Med Case Rep J*. 2021;14:711–7. [PMID: 34629908].
12. Leung VC, Antonios R, Désy D, Rahal A, Boulos PR. A case of complete spontaneous regression of extensive Merkel cell carcinoma involving the orbit. *Can J Ophthalmol J Can Ophtalmol*. 2021;56:e13–5. [PMID: 32853590].
13. Warnick M, Singh S, Boisvert ME, Peck GL. Merkel cell carcinoma presenting as lymphadenopathy without a primary cutaneous lesion: a report of two cases. *Arch Dermatol*. 2008;144:1397–8. [PMID: 18936413].
14. de Zeeuw S, Schouten van der Velden AP, de Wilt HJHW, Wetzels CT a. H, Bonenkamp HJJ. A Merkel cell carcinoma presenting as a solitary lymph node metastasis without a primary lesion. Report of a case and review of the literature. *Acta Chir Belg*. 2012;112:317–21. [PMID: 23009000].
15. Szabó A, Richter I, Frydrychová D, Saláková M, Jirásek T. [Lymph node metastasis of Merkel cell carcinoma without known cutaneous primary - case report]. *Cesk Patol*. 2017;53:135–8. [PMID: 28937781].
16. Longo R, Balasanu O, Chastenot de Castaing M, et al. A Spontaneous Regression of an Isolated Lymph Node Metastasis from a Primary Unknown Merkel Cell Carcinoma in a Patient with an Idiopathic Hyper-Eosinophilic Syndrome. *Am J Case Rep*. 2018;19:1437–40. [PMID: 30510152].
17. Kervarrec T, Zaragoza J, Gaboriaud P, et al. Merkel cell carcinoma of lymph nodes without a skin primary tumor: A potential metastatic neoplasia associated with a brisk immune response. *J Am Acad Dermatol*. 2020;83:1789–92. [PMID: 32278804].
18. Eusebi V, Capella C, Cossu A, Rosai J. Neuroendocrine carcinoma within lymph nodes in the absence of a primary tumor, with special reference to Merkel cell carcinoma. *Am J Surg Pathol*. 1992;16:658–66. [PMID: 1530107].
19. Fotia G, Barni R, Bellan C, Neri A. Lymph nodal Merkel cell carcinoma: primary or metastatic disease? a clinical case. *Tumori*. 2002;88:424–6. [PMID: 12487565].
20. Rastrelli M, Del Fiore P, Buja A, et al. A Therapeutic and Diagnostic Multidisciplinary Pathway for Merkel Cell Carcinoma Patients. *Front Oncol*. 2020;10:529. [PMID: 32351898].
21. Kervarrec T, Tallet A, Miquelestora-Standley E, et al. Diagnostic accuracy of a panel of immunohistochemical and molecular markers to distinguish Merkel cell carcinoma from other neuroendocrine carcinomas. *Mod Pathol Off J U S Can Acad Pathol Inc*. 2019;32:499–510. [PMID: 30349028].
22. Reddi DM, Puri PK. Expression of focal TTF-1 expression in a case of CK7/CK20-positive Merkel cell carcinoma. *J Cutan Pathol*. 2013;40:431–3. [PMID: 23330966].
23. Harms PW, Collie AMB, Hovelson DH, et al. Next generation sequencing of Cytokeratin 20-negative Merkel cell carcinoma reveals ultraviolet-signature mutations and recurrent TP53 and RB1 inactivation. *Mod Pathol Off J U S Can Acad Pathol Inc*. 2016;29:240–8. [PMID: 26743471].

24. Miner AG, Patel RM, Wilson DA, et al. Cytokeratin 20-negative Merkel cell carcinoma is infrequently associated with the Merkel cell polyomavirus. *Mod Pathol Off J U S Can Acad Pathol Inc.* 2015;28:498–504. [PMID: 25394777].
25. Dabner M, McClure RJ, Harvey NT, et al. Merkel cell polyomavirus and p63 status in Merkel cell carcinoma by immunohistochemistry: Merkel cell polyomavirus positivity is inversely correlated with sun damage, but neither is correlated with outcome. *Pathology (Phila).* 2014;46:205–10. [PMID: 24614722].
26. Pang C, Sharma D, Sankar T. Spontaneous regression of Merkel cell carcinoma: A case report and review of the literature. *Int J Surg Case Rep.* 2015;7C:104–8. [PMID: 25603307].
27. Kervarrec T, Zaragoza J, Gaboriaud P, et al. Differentiating Merkel cell carcinoma of lymph nodes without a detectable primary skin tumor from other metastatic neuroendocrine carcinomas: The ELECTHIP criteria. *J Am Acad Dermatol.* 2018;78:964–972.e3. [PMID: 29180096].
28. Kotteas EA, Pavlidis N. Neuroendocrine Merkel cell nodal carcinoma of unknown primary site: management and outcomes of a rare entity. *Crit Rev Oncol Hematol.* 2015;94:116–21. [PMID: 25573607].
29. Pan Z, Chen Y-Y, Wu X, et al. Merkel cell carcinoma of lymph node with unknown primary has a significantly lower association with Merkel cell polyomavirus than its cutaneous counterpart. *Mod Pathol Off J U S Can Acad Pathol Inc.* 2014;27:1182–92. [PMID: 24406862].
30. Villani A, Fabbrocini G, Costa C, Carmela Annunziata M, Scalvenzi M. Merkel Cell Carcinoma: Therapeutic Update and Emerging Therapies. *Dermatol Ther.* 2019;9:209–22. [PMID: 30820877].
31. Patel P, Hussain K. Merkel cell carcinoma. *Clin Exp Dermatol.* 2021;46:814–9. [PMID: 33252781].
32. Schadendorf D, Lebbé C, Zur Hausen A, et al. Merkel cell carcinoma: Epidemiology, prognosis, therapy and unmet medical needs. *Eur J Cancer Oxf Engl 1990.* 2017;71:53–69. [PMID: 27984768].