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The Genomic Era of Merkel Cell Carcinoma: Advances in Accurate Diagnosis and New Therapeutic Opportunities

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ABSTRACT
Though rare, MCC is a very aggressive kind of skin cancer. The finding that UV-induced DNA destruction and the potential Merkel cell polyomavirus drove MCC's oncogenesis helped explain its biology. Among the strong indicators of MCC's immunogenic traits are the high incidence of immunosuppression in affected individuals and the existence of MCPyV-specific T cells, as well as lymphocytes with an "exhausted" phenotype in the tumor micro-environment. Immunotherapy has changed the management of advanced MCC patients with anti-PD-1/PD L1 suppression when used as first-line therapy, producing objective responses in up to 50–70% of cases. Many individuals, meanwhile, could develop an acquired resistance or contraindications towards immune checkpoint inhibitors, which would need the creation of creative treatment strategies. This paper will discuss present guidelines for treatment for MCC in addition to possible therapeutic viewpoints for advanced disease, concentrating on molecular pathways, targeted therapies, and immune-based strategies.
KEYWORDS: Epidemiology and pathogenesis, immune checkpoint inhibitors (ICI), Merkelcell polyomavirus (MCPyV), MCC.

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I. INTRODUCTION

A clinically significant condition, Merkel Cell Carcinoma (MCC) is a rare & aggressive cutaneous neuroendocrine carcinoma with great metastatic potential, fast progression, and high death rates. Cyril Toker originally noted this as being a "trabecular carcinoma on the skin" in 1972. It is significantly higher among immunocompromised individuals. Identifying and treating MCC successfully is still somewhat challenging among malignancies. MCC often causes a delayed diagnosis because of its unclear appearance. Usually, it appears as a fast-growing, painless lump on the skin when exposed to UV radiation. Though sometimes inadequate for advanced stages, traditional therapies, including surgical excision and radiation, provide limited control. Recent developments in immunotherapy, especially immune checkpoint inhibitors including nivolumab, pembrolizumab, as well as avelumab, have changed treatment and shown remarkable efficacy in generating long-lasting responses and higher survival rates in settings of advanced and metastatic conditions. [1] Dermatological oncologists in both the clinical and scientific fields have become increasingly interested in this entity in recent years because of its growing frequency, important new pathogenesis findings, and unmatched treatment option developments. Chemotherapy was the only treatment for advanced-stage or simply ineffective MCC before several clinical trials demonstrated the efficacy of immune-checkpoint inhibitors. These cancers were thought to come from Merkel cells, the only type of cutaneous cells producing granules & part of the amine precursors uptake & decarboxylation system (APUD) system. Especially, there is somewhat fresh proof that Merkel cells are derived from the pluripotent epidermal stem cells. HIV-infected patients and organ transplant recipients are far more likely to acquire MCC (12/100,000/years) and at a far younger age (about 50% <50 years). In the development of MCC, UV radiation is believed to have an immune-suppressive effect instead of a mutagenic or carcinogenic one. Avelumab, which several authorities approved in 2017, was the first drug to be approved for metastatic MCC. Among the risk elements are old age, fair skin, suppression of immunity, and UV exposure. Essential therapeutic steps are surgery, adjuvant, or as therapeutic radiation, and for more advanced, incurable phases, medication-assisted treatment of the tumor. Modern diagnostic technologies—including CT DNA assays and sentinel lymphatic node biopsy—help to improve early detection and monitoring. Immune checkpoint inhibitors such as avelumab, pembrolizumab, and nivolumab have transformed the therapy scene with

their capacity to generate long-lasting impacts and higher survival.

II. EPIDEMIOLOGY AND PATHOGENESIS OF MERKEL CELL CARCINOMA

A rare superficial tumor, Merkel cell carcinoma, accounts for less than one percent of all non-melanocytic skin malignancies in Germany. Incidence varies greatly by geography. Australia's rate is the highest at 1.6–2.5 per million person years; the USA comes next at 0.66–0.79 and New Zealand at 0.88–0.96. By comparison, MCC is less prevalent in Europe, where rates can vary between 0.2 - 0.3 for every 100,000 person-years [2]. More common in men, MCC mostly impacts fair-skinned individuals who expose the sun for long periods. Recognized risk factors include an advanced age (such as >75 years) & immune deficiency (e.g., from organ donation or as chronic lymphocytic leukemia (CLL)). [3] About 80% of MCCs in the northern part of the world are caused by MCPyV, the main etiopathogenetic agent. UV radiation is the main etiopathogenetic cause of MCC in Australia. Since its first reporting, MCC has been slowly increasing globally. Epidemiological research shows that annual rates are rising by 2–4%, which is comparable to a 3 to 5 factor increase in cases that are newly identified yearly over the last few decades. The cell where MCC originally emerged is unknown. Because they have undergone terminal differentiation, usual Merkel cells are no longer been believed to be the origin of the cancer [4]. The tumor's dual source has inspired several theories. [3,17,18] MCPyV-positive MCCs are thought to come from epithelial cells, dermal stem cells of mesenchymal origin, fibroblasts, and pro-B/pre-B lymphocytes. Though outside the scope of this article, pro-B/pre- B cell lineage arguments comprise the IHC generation of immunoglobulins along with B-cell markers (like TdT & PAX-5) through virus-positive MCCs, or, as well as the sporadic display of IgH and IgK. Moreover, reports indicate that MCC has shrunk following treatment with idelalisib, a drug for B-cell lymphoma and leukemia. [17] MCPyV-negative neoplasm which are pathogenetically and sometimes morphologically linked to squamous cell cancer are thought to arise from aberrant malignant cell transformation keratinocytes (such as from cancer stem cells which can differentiate in several directions or as the result of combined genetic "hits" resulting in a change from a cutaneous to a high-grade neural endocrine phenotype). Though men are somewhat more likely than women to get Merkel cell carcinomas, percentages of each gender differ worldwide. In several European countries, the proportion of female patients is greater (54–69%) compared to the percentage of the male population (59–68%) in the United States and Australia. Fair-skinned people are significantly more likely to get MCC than African-American, Asian counterparts.

III. CLINICAL FEATURES OF MERKEL CELL CARCINOMA

MCC usually appears on the head or neck of an older, white patient who has been sun-damaged. It often, nonetheless, affects areas sheltered from sunlight, such as the limbs and trunk. Mucosal membranes are rarely affected. [21] The clinical presentation of MCC is a fast-growing, pain-free, erythematous/violaceous nodule and plaque. [19]

The acronym AEIOU captures these traits:
Afoasymptomatic, E for fast rising, I as immune suppression, O for older than 50, and
U stands for UV-exposed area. [20]

Clinically, the tumor is hard to identify; it has to be looked at under a microscope. The main elements known to be involved in the pathogenesis of MCC are UV radiation, as shown by a to an eight-fold greater tendency for white people compared to black people, a relationship between incidence & UVB irradiation index, the highest rates of incidence in Australia and a preponderance to sun-exposed skin. [22] HIV patients, as well as transplant recipients, show immunosuppression by a significantly increased risk. [23,24] and the more recent discovery that better survival is connected to strong intra-tumoral T-lymphocyte infiltrates. [25,26] So far, no research has been done on the exact control of immunosuppressive treatment in transplant patients with MCC; therefore, reducing immunosuppressive drugs should be addressed on a personal level. Molecular techniques reveal the DNA of the typical virus identified as Merkel cell polyomavirus (MCPyV) in up to 80% of cases; recently created monoclonal antibody targeting the large T antigen reveals it in 97% of instances. [27,28,29]

IV. HISTOPATHOLOGICAL FEATURES

Under a microscope, MCC is classified as a "little blue round cell cancer" in the epidermis subcutis. Rarely is the epidermis impacted. Uncommon are MCCs mostly or entirely intraepidermal. The tumor cells show a high nuclear: cytoplasmic ratio, ambiguous nucleoli, and a "salt as well as pepper" nuclear chromatin pattern. Usually, they are in nests along with sheets. Though it was once called "trabecular carcinoma," the trabecular sequence is unusual and usually focal when it does appear. Sometimes, so-called Homer-Wright-like pseudo-rosettes might be seen.[49] Many mitotic figures, randomly apoptotic cells, and sporadic geographic necrosis sites can be found. Although

MCC is no longer divided by trabecular, intermediate, and small cell types as it had been in the past, MCPyV negative cells have been Related to larger-cell cytomorphology and the uncommon appearance of pleomorphic and possibly clear cells. Though some instances exhibit extra mixed sarcomatous and/or carcinomatous characteristics, most MCCs have pure neuroendocrine phenotype/"pure MCCs." These are known as "combined MCCs." Squamous differentiation is the most often observed "divergent" feature.[4] Among the appearances are: (i) connection between an invasive carcinoma of squamous cells and a small blue round cell neuroendocrine tumor, as well as their overlap. (ii)Rarely, a small, round, blue neuroendocrine carcinoma with differentiated squamous foci appears. (iii)As an intraepidermal growth of malignant neuroendocrine tissues while Bowen disease is present. Epidermotropism & adnexotropism are more often encountered in conjunction than in pure MCCs. [7]

V. INVESTIGATIONAL THERAPIES IN MCC

Immunotherapies: Several studies suggested that ICI would help MCC patients. Most likely resulting from immune stimulation, MCC spontaneous reversal is an uncommon but well-studied phenomenon. Those whose cancers lack infiltrating lymphocytes do worse than those with MCCs with T cell invasion. The abscopal impact of irradiation—where specific radiation therapy is connected to a regression of additional tumor areas beyond the treatment field— has additionally been observed in MCC patients, suggesting a controlled immune response.[6] MCCs are more frequent and have a worse prognosis when there is immune impairment. Finally, as they show either MCPyV antigens /ultraviolet-mutation-associated neoantigens, MCCs are possible targets for antitumor immunotherapy.[8] Both the natural and adaptive parts of the immune system may be antitumor. Adaptive antitumor immunity is regulated by proteins generated on the outermost layer of both immune cells as well as tumor cells, hence mediating effector T cell activation by antigen-presenting cells. Among the several signalling routes that could activate the immune system are theOX40–OX40L & CD137–4–1BBL axes. Other signalling pathways, including the cytotoxic T lymphocyte antigen 4 (CTLA-4) along with apoptosis protein 1 (PD-1)–PD-L1 immunological checkpoints, allow tumor cells to escape the immune system and suppress immune responses. Immunotherapies thus either activate or suppress inhibitory pathways to boost anticancer immunity.[9] Of these, PD-1–PD-L1 immune checkpoint suppression has drawn the most attention in MCC. PD-1–PD-L1 immune checkpoint suppression has become the subject of thorough investigations in MCC. [47]

Targeted therapies, Immunosuppressed or non-responding advanced-stage MCC patients need alternatives to ICI. A range of targeted therapy kinds have been investigated in MCC cell lines & xenograft models; some are now undergoing additional testing in early phase clinical trials. YM155 safely kills cells in VP-MCC cell lines and xenografts. [10,11] Likewise, ABT-263 - Inhibitor for the apoptosis controller BCL-2 family members induces apoptosis in most MCC cell lines investigated, regardless of MCPyV status.[12] Though xenograft studies show BCL-2 antisense oligonucleotides to be effective, other patients showed no advantage. Though some patients showed no improvement with BCL-2 antisense oligonucleotides [47].

Radiotherapy (RT) can be a palliative option for MCC patients who are incurable or an adjuvant treatment following surgery, since MCC is considered a radiosensitive malignancy. On the other hand, radiation monotherapy could not yield the same outcomes as complete surgical excision. Retrospective studies of 43 patients showed a comparable result with an overall survival percentage of 37%. A retrospective analysis of 57 ineffective patients treated by targeted radiation therapy demonstrated a 5-year as a whole survival rate of 39%. [50] The NCCN guidelines to obtain radiation with a therapeutic goal indicate doses within 60 and 66 Gy and a wide therapy perimeter (5 cm) around the primary location. Radiation doses to the primary site following surgical resection should range between 50 and 60 Gy, depending upon whether microscopically positive margins have been detected or not. [5]

VI. CURRENT TREATMENT OPTIONS IN MCC

The therapy choice is determined by the tumor features—such as stage of presentation, regional lymph node involvement, disease situated, multiple medical conditions, and patient performance status. [13-15] Current treatment strategies involving surgery and/or radiation therapy, despite their great locoregional control rates, are often connected to the emergence of distant metastases. Although chemotherapy has had little efficacy in treating metastatic disease, improvements in immunotherapies are expected to greatly affect the management and outcomes of MCC. Treatment choices are often based on data from prospective randomized controlled trials and retrospective series, since there are now no authorized therapeutic agents for the treatment of the advanced form of MCC.

Options for treatment for the loco-regional form have been extensively established. In the metastatic setting, chemotherapy is of little use; nevertheless, advances in Immunotherapeutics are expected to greatly influence MCC management and outcomes. [48]

VII. PRESENTATION AND DIAGNOSIS

Usually, MCC appears as the red/violaceous nodule developing rapidly on an older, lighter in complexion person's sun-exposed skin. As many as 15 percent of MCC patients, however, will present having a tumor-positive lymph node but no obvious cutaneous tumor; this is probably caused by metastatic disease where the skin under the tumor has faded. [30,38,42] A diagnosis of MCC has to be confirmed by means of histopathological and immunohistochemical findings.[30] MCC could also be confused with basal-cell Cancer.[43] Thus, the diagnosis has to be confirmed using immunohistochemistry techniques [43]. Immunohistochemistry studies are thus essential to confirm the diagnosis. Though not particular signs, neuroendocrine markers like synaptophysin or chromogranin A frequently express themselves by MCCs. Usually as paranuclear spots, cytoplasmic along with membrane patterns, or both, most MCCs exhibit cytokeratin 20 (CK20) focally or diffusely. The staining process for neurofilament, another intermediary filament, reveals a paranuclear dot-like pattern as well. CK20 conveying & the paranuclear dot-like appearance of intermediate filament staining clearly point to MCC.[30] The synoptic reporting of newly diagnosed lesions facilitates treatment decisions and prognostic studies by at least including, the peripheral & deep margin status and the level of lymph vascular invasion as well as extracutaneous extension (bone, muscle, fascia and/or cartilage involvement).[44] Morphologically, MCC and metastatic SCLC are identical. Morphologically, MCC and cancerous SCLC are identical. Expressions vary, hence no one marker by itself is prone or particular enough to consistently separate MCC through metastatic SCLC. A collection of markers is thus necessary, particularly for the identification of challenging circumstances such as CK20-negative MCC. Moreover, several non-lung SmCCs, such as parotid alongside uterine cervical original cancers, often have CK20 as well. Consequently, particularly where metastatic MCC has migrated to an unknown source location, they could be more difficult to distinguish from MCC.[30] It can be especially challenging to tell primary parotid SmCC from metastatic MCC of unknown origins since the parotid is usually a site of regional MCC spread & primary parotid SmCC is rare. [45] As NGS-based methods become more common, MCPyV detection and mutational signature analysis may help distinguish metastatic SCLC (MCPyV-negative along with smoking signature mutations) from MCC (MCP+ or UV signature mutations).[41] For example, UV signature mutations discovered in a parotid gland tumor confirmed the presence of metastatic MCC of unidentified initial origin rather than a main parotid neuroendocrine carcinoma [39]. Distant cutaneous metastases are possible in patients with MCC. Patients with MCC may have distant cutaneous metastases. Studies of clonality depending on copy number changes, mutations, and/or MCPyV sequencing could help distinguish cancer that has spread from a second primary MCC among patients who present having a rare second cutaneous MCC that is spatially and temporally separated from the first primary MCC such that the tumor is scientifically designated a second primary. [40, 46]

VIII. MANAGEMENT OF MCC

Usually followed with radiation therapy, surgical excision with 1-2 cm margins treats primary MCCs. Though adjuvant radiotherapy to the main tumor site is often recommended, in a subgroup of individuals (such as those with malignancies), the morbidity issues related with radiotherapy can be avoided with a low local recurrence rate. Currently, immunohistochemistry For broad-spectrum cytokeratin's and/or CK20 is often used to boost the identification of micro metastases in sentinel lymph nodes since any size of metastatic deposit is considered positive with reference to nodal staging. [33,31] Because any size of metastatic deposit is considered positive with reference to nodal staging, broad-spectrum cytokeratin and/or CK20 immunohistochemistry is often used now to boost the detection of micro metastases in sentinel lymph nodes. [30, 34] To manage clinically detectable or hidden nodal disease, the NCCN recommends using imaging testing for distant metastases, then lymph node dissection and/or radiation treatment to the nodal basin. [32] Historically, patients with MCC have been treated systemically with chemotherapy, platinum-based drugs, taxanes, anthracyclines, and etoposides.[35] Avelumab, an anti-PD-L1 antibody, has been approved by the European Medicines Agency (EMA), Swiss medic, the FDA, and the Japanese Ministry of Health, Labor, and Welfare as a therapy for metastatic MCC in the previous two years [36]. Three dozen other immunotherapies that are for MCC also demonstrated promise in clinical studies. [37] The efficacy of (ICI) is a key turning point in the therapy of advanced-stage MCC. Not every patient, however, reacts to ICI in a long-lasting manner. Furthermore, ICI might not be the ideal choice for people with autoimmune disorders or those requiring immunosuppression as recipients of solid transplanted organs. As a result, present research objectives in MCC patients are predicting and

boosting immunotherapy response as well as identifying alternative treatments for those for whom ICI is unsuitable and/or unsuccessful.

IX. CONCLUSION

Immunotherapy and ICI have transformed the standard approach for treating locally advanced or metastatic MCC substantially. Chemotherapy is considered nowadays to be palliative; any responses are transient. In the majority of patients, it's impossible to identify tumor-specific driver mutations and the inadequate efficacy of targeted therapies like monotherapy can be attributed to the broad range in the oncogenesis of metastatic colorectal cancer (MCC). Improving the clinical management of MCC would be the establishment of a cooperative architecture enabling rapid planning and execution of clinical investigations, as well as formal information sharing. In a disease with such low frequency, this element is quite crucial. Though there are still major scientific challenges to be addressed, our understanding of MCC in the biological sciences, diagnosis, and therapy has much advanced. Furthermore, the origin of the MCC cell was unknown. Finally, more therapeutic options have to be validated if the advantages of radiation, surgery, and immunotherapy are to be further increased, thereby guiding patient outcomes. [16,5]

REFERENCE

[1]. Marka S, Konga J, Ponnala P, Navigating Recent Progressions in Merkel Cell Carcinoma, Journal of Drug Delivery and Therapeutics. 2025; 15(3):168-179 DOI: http://dx.doi.org/10.22270/jddt.v15i3.7045.

[2]. Weilandt J, Peitsch WK. Modern diagnostics and treatment of Merkel cell carcinoma. JDDG: Journal der Deutschen Dermatologischen Gesellschaft. 2023; 21: 1524–1546. https://doi.org/10.1111/ddg.15214.

[3]. Harms PW, Harms KL, Moore PS, et al. The biology and treatment of Merkel cell carcinoma: current understanding and research priorities. Nat Rev Clin Oncol. 2018;15(12):763-776. https://doi.org/10.1038/s41571-018-0103-2.

[4]. Walsh NM, Cerroni L. Merkel cell carcinoma: A review. J Cutan Pathol. 2021; 48(3): 411–421. https://doi.org/10.1111/cup.13910.

[5]. Merkel Cell Carcinoma—Update on Diagnosis, Management and Future Perspectives. Cancers 2023, 15(1), 103; https://doi.org/10.3390/cancers15010103

[6]. Cotter, S. E. et al. Abscopal effect in a patient with metastatic Merkel cell carcinoma following radiation therapy: potential role of induced antitumor immunity. Arch. Dermatol. 147, 870–872 (2011).

[7]. Busam, K.J.; Jungbluth, A.A.; Rekthman, N.; Coit, D.; Pulitzer, M.; Bini, J.; Arora, R.; Hanson, N.; Tassello, J.A.; Frosina, D.; et al. Merkel cell polyomavirus expression in merkel cell carcinomas and its absence in combined tumors and pulmonary neuroendocrine carcinomas. Am. J. Surg. Pathol. 2009, 33, 1378–1385. [CrossRef]

[8]. Cassler, N. M., Merrill, D., Bichakjian, C. K. & Brownell, I. Merkel cell carcinoma therapeutic update. Curr. Treat. Opt. Oncol. 17, 36 (2016).

[9]. Torphy, R. J., Schulick, R. D. & Zhu, Y. Newly emerging immune checkpoints: promises for future cancer therapy. Int. J. Mol. Sci. 18, 2642 (2017).

[10]. Arora, R. et al. Survivin is a therapeutic target in Merkel cell carcinoma. Sci. Transl Med. 4, 133ra56 (2012).

[11]. Dresang, L. R. et al. Response of Merkel cell polyomavirus-positive merkel cell carcinoma xenografts to a survivin inhibitor. PLOS ONE 8, e80543 (2013)

[12]. Verhaegen, M. E. et al. Merkel cell carcinoma dependence on Bcl-2 family members for survival. J. Invest. Dermatol. 134, 2241–2250 (2014).

[13]. Harms PW. Update on Merkel Cell Carcinoma. Clin Lab Med. 2017;37(3):485–501.

[14]. Harms PW, Harms KL, Moore PS, et al. International Workshop on Merkel Cell Carcinoma Research (IWMCC) Working Group. The biology and treatment of Merkel cell carcinoma: current understanding and research priorities. Nat Rev Clin Oncol. 2018;15(12):763–76. https://doi.org/10.1038/s41571-018-0103-2.

[15]. Banks PD, Sandhu S, Gyorki DE, Johnston ML, Rischin D. Recent Insights and Advances in the Management of Merkel Cell Carcinoma. J Oncol Pract. 2016;12(7):637–46.

[16]. Allen, P.J.; Bowne, W.B.; Jaques, D.P.; Brennan, M.F.; Busam, K.; Coit, D.G. Merkel cell carcinoma: Prognosis and treatment of patients from a single institution. J. Clin. Oncol. 2005, 23, 2300–2309. [CrossRef].

[17]. Pietropaolo V, Prezioso C, Moens U. Merkel cell polyomavirus and Merkel cell carcinoma. Cancers (Basel).2020;12(7):1774. https://doi.org/10.3390/cancers12071774.

[18]. Kervarrec T, Samimi M, Guyetant S, et al. Histogenesis of Merkel cell carcinoma: a comprehensive review. Front Oncol.

2019; 9:1-13. https://doi.org/10.3389/fonc.2019.00451.
[19]. Becker JC, Stang A, DeCaprio JA, et al. Merkel cell carcinoma. Nat Rev Dis Primers. 2017; 3:17077. https://doi.org/10.1038/nrdp. 2017.77.
[20]. Heath M, Jaimes N, Lemos B, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. J Am Acad Dermatol. 2008;58(3):375-381. https://doi.org/10.1016/j.jaad. 2007.11.020.
[21]. Harms KL, Healy MA, Nghiem P, 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- 3571. https://doi.org/10.1245/s10434- 016-5266-4.
[22]. Agelli M, Clegg LX. Epidemiology of primary Merkel cell carcinoma in the United States. J Am Acad Dermatol 2003;49(5):832–41.
[23]. Lanoy E, Costagliola D, Engels EA. Skin cancers associated with HIV infection and solid-organ transplantation among elderly adults. Int J Cancer 2010;126(7):1724–31.
[24]. Koljonen V, Kukko H, Tukiainen E, Bohling T, Sankila R, Pukkala E, et al. Incidence of Merkel cell carcinoma in renal transplant recipients. Nephrol Dial Transplant 2009;24(10):3231–5.
[25]. Sihto H, Kukko H, Koljonen V, Sankila R, Bohling T, Joensuu H. Clinical factors associated with Merkel cell polyomavirus infection in Merkel cell carcinoma. J Natl Cancer Inst 2009;101(13):938–45.
[26]. Sihto H, Bohling T, Kavola H, Koljonen V, Salmi M, Jalkanen S, et al. Tumor infiltrating immune cells and outcome of Merkel cell carcinoma: a population-based study. Clin Cancer Res 2012;18(10):2872–81.
[27]. Kassem A, Technau K, Kurz AK, Pantulu D, Loning M, Kayser G, et al. Merkel cell polyomavirus sequences are frequently detected in nonmelanoma skin cancer of immunosuppressed patients. Int J Cancer 2009;125(2):356–6.
[28]. Paik JY, Hall G, Clarkson A, Lee L, Toon C, Colebatch A, et al. Immunohistochemistry for Merkel cell polyomavirus is highly specific but not sensitive for the diagnosis of Merkel cell carcinoma in the Australian population. Hum Pathol 2011;42(10):1385–90.
[29]. Rodig SJ, Cheng J, Wardzala J, Do Rosario A, Scanlon JJ, Laga AC, et al. Improved detection suggests all Merkel cell carcinomas harbor Merkel polyomavirus. J Clin Invest 2012;122(12):4645–53.
[30]. Harms, P. W. Update on Merkel cell carcinoma. Clin. Lab. Med. 37, 485–501 (2017)
[31]. Cassler, N. M., Merrill, D., Bichakjian, C. K. & Brownell, I. Merkel cell carcinoma therapeutic update. Curr. Treat. Opt. Oncol. 17, 36 (2016).
[32]. Bichakjian, C. K. et al. Merkel cell carcinoma, version 1.2018, NCCN clinical practice guidelines in oncology. J. Natl Compr. Canc. Netw. 16, 742–774 (2018).
[33]. Frohm, M. L. et al. Recurrence and survival in patients with Merkel cell carcinoma undergoing surgery without adjuvant radiation therapy to the primary site. JAMA Dermatol. 152, 1001–1007 (2016).
[34]. Su, L. D. et al. Immunostaining for cytokeratin 20 improves detection of micrometastatic Merkel cell carcinoma in sentinel lymph nodes. J. Am. Acad. Dermatol. 46, 661–666 (2002).
[35]. Nghiem, P. et al. Systematic literature review of efficacy, safety and tolerability outcomes of chemotherapy regimens in patients with metastatic Merkel cell carcinoma. Future Oncol. 13, 1263–1279 (2017).
[36]. Baker, M., Cordes, L. & Brownell, I. Avelumab: a new standard for treating metastatic Merkel cell carcinoma. Expert Rev. Anticancer Ther. 18, 319–326 (2018).
[37]. Nghiem, P. T. et al. PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. N. Engl. J. Med. 374, 2542–2552 (2016).
[38]. Becker, J. C. et al. Merkel cell carcinoma. Nat. Rev. Dis. Primers 3, 17077 (2017).
[39]. Harms, P. W. et al. The distinctive mutational spectra of polyomavirus-negative Merkel cell carcinoma. Cancer Res. 75, 3720–3727 (2015).
[40]. Harms, K. L. et al. Multiple primary Merkel cell carcinoma: molecular profiling to distinguish genetically distinct tumors from clonally related metastases. JAMA Dermatol. 153, 505–512 (2017).
[41]. Harms, P. W. et al. Next generation sequencing of cytokeratin 20-negative Merkel cell carcinoma reveals ultraviolet-signature mutations and recurrent TP53 and RB1 inactivation. Mod. Pathol. 29, 240–248 (2016).
[42]. Vandeven, N. A. et al. Merkel cell carcinoma patients presenting without a primary lesion have elevated markers of immunity, higher tumor mutation burden and improved survival. Clin. Cancer Res. 24, 963–971 (2017).
[43]. Ball, N. J. & Tanhuanco-Kho, G. Merkel cell

carcinoma frequently shows histologic features of basal cell carcinoma: a study of 30 cases. J. Cutan. Pathol. 34, 612–619 (2007).

[44]. Bichakjian, C. K. et al. Merkel cell carcinoma, version 1.2018, NCCN clinical practice guidelines in oncology. J. Natl Compr. Canc. Netw. 16, 742–774 (2018).

[45]. Chernock, R. D. & Duncavage, E. J. Proceedings of the NASHNP Companion Meeting, March 18th, 2018, Vancouver, BC, Canada: salivary neuroendocrine carcinoma — an overview of a rare disease with an emphasis on determining tumor origin. Head Neck Pathol. 12, 13–21 (2018).

[46]. Schrama, D. et al. Distinction of 2 different primary Merkel cell carcinomas in 1 patient by Merkel cell polyomavirus genome analysis. Arch. Dermatol. 146, 687–689 (2010).

[47]. Harms, P.W., Harms, K.L., Moore, P.S. et al. The biology and treatment of Merkel cell carcinoma: current understanding and research priorities. Nat Rev Clin Oncol 15, 763– 776 (2018). https://doi.org/10.1038/s41571-018-0103-2

[48]. Villani, A., Fabbrocini, G., Costa, C. et al. Merkel Cell Carcinoma: Therapeutic Update and Emerging Therapies. Dermatol Ther (Heidelb) 9, 209–222 (2019). https://doi.org/10.1007/s13555-019-0288-z

[49]. Tang C-K, Toker C. Trabecular carcinoma of the skin: an ultrastructural study. Cancer. 1978;42(5):2311-2321. https://doi.org/10.1002/ 1097-0142(197811) 42:53.0.co;2-l.

[50]. Veness M, Foote M, Gebski V, Poulsen M. The role of radiotherapy alone in patients with Merkel cell carcinoma: reporting the Australian experience of 43 patients. Int J Radiat Oncol. 2010; 78:703–9.