

Merkel Cell Carcinoma: A Review

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PRACTICE POINTS

- Merkel cell carcinoma has been associated with a novel polyomavirus.
- Merkel cell carcinoma follows a very aggressive course and is most likely metastatic at diagnosis.

Merkel cell carcinoma (MCC) is a rare neuroendocrine tumor of unknown origin that usually presents in the elderly population. A novel polyomavirus has been associated with a large percentage of tumors. Immune response plays an important role in pathogenesis of MCC. This article reviews the history, pathogenesis, presentation, and treatment of MCC. Future treatments also are discussed briefly.

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Merkel cells originally were described by German histopathologist Friedrich Sigmund Merkel in 1875. These unique tactile cells were described as epidermal, nondendritic, and non-keratinizing. Merkel cells are thought to arise from the neural crest and are believed to be primary neural cells found within the basal layer of the epidermis.^{1,2} They likely function primarily as slowly adapting type I mechanoreceptors. Origin from the neural crest is controversial, as other investigators have suggested derivation from epidermal keratinocytes.^{1,2}

Tumor cells have been linked to the amine precursor uptake and decarboxylation system.³ In 1972, Toker⁴ described several cases of trabecular or sweat gland carcinomas of the skin. Upon further investigation, the cells that comprised these tumors were found to have dense core granules on electron microscopy, typical of Merkel cells.^{1,2} Other terms such as *neuroendocrine carcinoma of the skin*, *small cell carcinoma of the skin*, and *anaplastic carcinoma of the skin* have been used to describe Merkel cell carcinoma (MCC),¹ which was suggested by De Wolf-Peeters et al⁵ in 1980.

Despite being a rare malignancy, MCC follows an aggressive clinical course. Upon presentation, approximately 66% of patients have local disease, 27% have nodal involvement, and 7% have distant metastasis.¹ Future treatments will likely center around the novel Merkel cell polyomavirus (MCPyV) and modification of immune responses toward tumor cells. Standardization continues to be lacking in both staging and treatment of this aggressive tumor.

Epidemiology of MCC

Between 1986 and 2006, the incidence of MCC grew substantially.^{1,2} Figures have been reported at 0.15 cases per 100,000 individuals to 0.6 cases per 100,000 individuals worldwide. In the United States, the age-adjusted incidence of MCC is estimated at 0.24 per 100,000 person-years, which is higher than the estimated 0.13 per 100,000 person-years found in Europe.³ The highest incidence worldwide has been noted in Western Australia, likely due to high levels of UV exposure.¹ The

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incidence of MCC in psoriasis patients who are treated with oral methoxsalen (psoralen) and UVA photochemotherapy is 100 times greater than in the general population, further supporting the role of UV light in the development of MCC.¹ White individuals have the highest incidence of MCC worldwide, with men being affected more frequently than women.^{1,3} The majority of patients with MCC are diagnosed at 70 years or older.¹ Approximately 5% of reported MCC patients are diagnosed before 50 years of age.² Immunosuppression and immunodeficiency likely play a role in the pathogenesis of MCC, and the incidence is increased in solid organ transplant recipients, most commonly renal transplant recipients,¹ as well as individuals with chronic lymphocytic leukemia, human immunodeficiency virus infection, and AIDS.^{1,3} Patients with autoimmune diseases such as rheumatoid arthritis also are at increased risk for MCC.³ Individuals who are diagnosed with MCC are at an increased risk for development of other malignancies including nonmelanoma skin cancers, chronic lymphocytic leukemia, Hodgkin lymphoma, and non-Hodgkin lymphoma.³

Clinical Presentation of MCC

The clinical presentation of MCC can be variable. Most tumors present as firm, red to purple, non-tender papules or nodules (Figure 1).¹ Tumor size may range from 2 to 200 mm but is most commonly less than 20 mm.² Growth can be rapid, and tumors are most commonly located on sun-exposed skin. The head and neck areas account for 48% of all MCC cases,¹ with the eyelids being frequently involved.² Merkel cell carcinoma also has been reported on the arms, legs, trunk, back, and buttocks.¹ Non-sun-exposed areas are less commonly affected. Mucosal sites (eg, larynx, nasal cavity, pharynx, mouth) account for 5% of primary MCCs.¹ Merkel cell carcinoma also has been reported to affect the vulva and penis. Subcutaneous primary MCC has presented without overlying epidermal changes.¹ In a case series by Heath et al,⁶ 14% (27/195) of MCC patients presented with nodal disease without any identifiable primary tumor, with the inguinal nodal chain being the most common for this presentation. It currently is not known whether these nodal tumors are primary tumors or metastatic disease with a regression of the primary tumor.¹

Histopathology of MCC

Merkel cells are small- to medium-sized basophilic cells with round nuclei and scant cytoplasm. Granular or stippled chromatin can be seen on histopathology (Figure 2A).¹ Some tumor cells have more vesicular chromatin, multiple small



Figure 1. A 2.3×1.5×1.2-cm, hemorrhagic, crusted, exophytic tumor on the left cheek.

nucleoli, irregular contours, and more abundant cytoplasm. In some reports, irregular contours and abundant cytoplasm were associated with no detectible MCPyV infection.^{1,3} Merkel cell carcinomas have a primarily nodular architecture, and classification is based on growth pattern and cell size. Three histopathologic growth patterns have been described: nodular, infiltrative, and trabecular. The trabecular pattern is composed of interconnecting strands of cells (Figure 2B). Tumors with solely intraepidermal involvement (MCC in situ) have been described but are exceedingly rare.¹ Cell types are classified according to size, with the intermediate cell type being the most common. The small cell variant may be mistaken for a lymphocytic infiltrate due to the similar size and appearance of both types of cells.^{1,3}

Merkel cell carcinomas can have histopathological overlap with lymphomas, small cell lung cancers, carcinoid tumors, primitive neuroectodermal tumors, neuroblastomas, small cell osteosarcomas, rhabdomyosarcomas, or Ewing sarcomas.^{1,3} Specifically, differentiation from small cell carcinoma of the lung is of utmost importance. Merkel cell carcinoma stains positively for cytokeratins 8, 18, 19, and 20. The neuroendocrine markers chromogranin (Figure 3A), synaptophysin, and neuron-specific enolase also may show positive

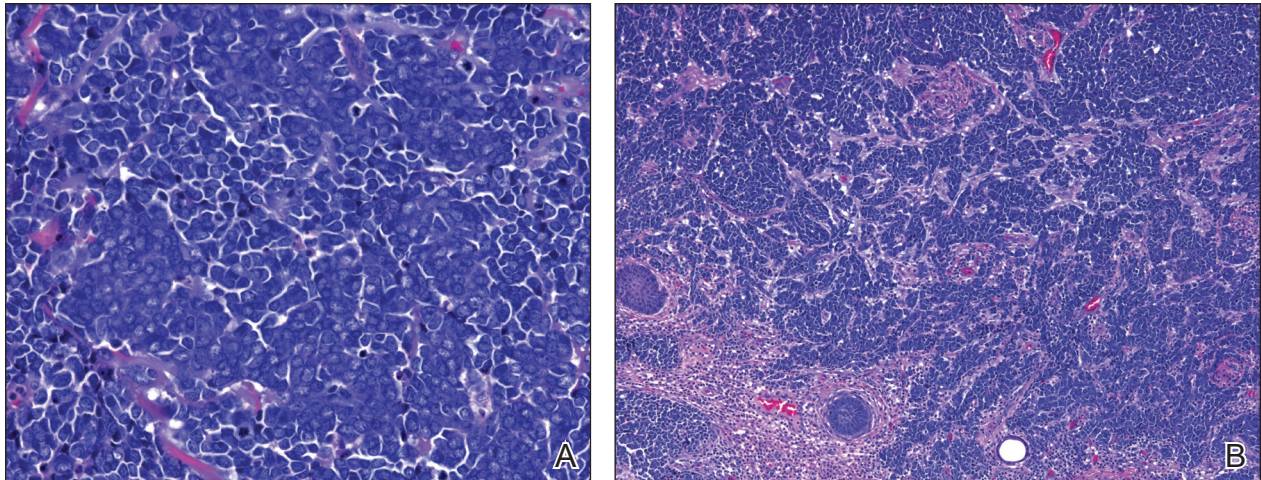


Figure 2. Merkel cells are small- to medium-sized cells with round nuclei and scant cytoplasm. Granular or stippled chromatin can be seen (A)(H&E, original magnification $\times 40$). Merkel cell carcinoma with trabecular pattern (B)(H&E, original magnification $\times 10$).

staining. Cytokeratin 20, low-molecular-weight cytokeratins (CAM 5.2), and neurofilament immunostains have a high sensitivity for MCC and are the most frequently used.¹ Cytokeratin 20 stains in the characteristic paranuclear dot-like pattern, which is a hallmark of MCC (Figure 3B). Cytokeratin 20 positivity in conjunction with negative staining for thyroid transcription factor 1 (Figure 3C) and cytokeratin 7 can aid in differentiation from small cell carcinoma of the lung.^{1,3}

Pathogenesis of MCC

In 2008, Feng et al⁷ discovered a novel polyomavirus associated with the development of MCC. This novel polyomavirus, MCPyV, is found in approximately 80% of all cases of MCC. Seventeen members of the polyomavirus family have been identified, 9 of which have been found to infect humans, including BK virus, JC virus, WU, MCPyV, human polyomavirus 6, human polyomavirus 7, trichodysplasia spinulosa-associated polyomavirus, human polyomavirus 9, and Simian virus 40.¹ Merkel cell polyomavirus infection is found in approximately 60% of the general population and exposure likely occurs early in life. The virus likely is transmitted through skin shedding and nasal secretions, though it also has been found in urine specimens.³ Currently, there is no evidence to suggest vertical viral transmission from mother to fetus.

Merkel cell polyomavirus is composed of early and late gene regions. The early gene region contains both large T antigen (LT) and small T antigen reading frames, which are necessary for viral replication.⁸

The late region is responsible for encoding viral proteins necessary for viral capsid assembly. Mutations found in viral protein 1 prevent formation of viral particles.⁹ Large T antigen is substantially overexpressed in MCC and is responsible for tumor suppression through retinoblastoma tumor suppressor protein. It also serves as a binding domain for both heat shock proteins and helicases.^{8,10} These domains allow the polyomaviruses to use host-cell machinery for viral genome replication while targeting tumor suppressor proteins.⁸ Upon viral integration into host DNA, viral replication ceases while oncogenic function persists.

The exact mechanism by which the MCPyV contributes to the development of MCC still has yet to be identified. Hypotheses suggest a combination of viral infection with external mutagens (eg, UV radiation). Experimental observations suggest viral contribution is likely due to the large percentage of MCCs that are positive for MCPyV, the identification of LT antigen expression and the role it plays in preserving cell cycle progression, and the role persistent LT antigen expression plays in continued growth of MCC cell lines in vitro.⁸ Two important cell line preservation mechanisms ensure continued tumor growth, including prevention of apoptosis triggered by DNA damage response mechanisms following UV damage and interaction with the retinoblastoma tumor suppressor protein allowing continued growth.^{8,11} Other important factors in tumor growth and survival may be the inhibition of apoptosis through the *BCL2* (B-cell chronic lymphocytic leukemia/lymphoma 2) proto-oncogene and

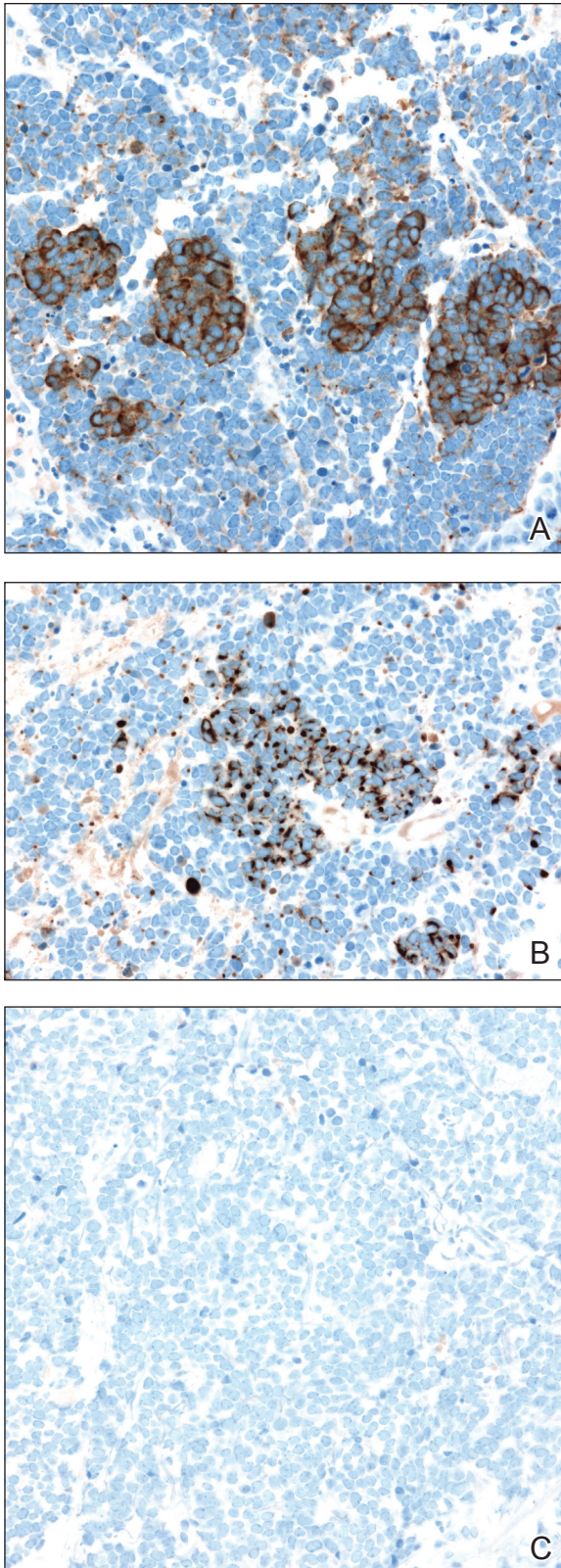


Figure 3. Positive chromogranin staining (A)(original magnification $\times 40$). Cytokeratin 20 staining in the characteristic paranuclear dot-like pattern (B)(original magnification $\times 40$). Negative thyroid transcription factor 1 staining (C) (original magnification $\times 40$).

survivin (baculoviral inhibitor of apoptosis repeat-containing 5 [BIRC5]).¹² Survivin has been found to play an important role in MCPyV-positive MCCs.^{12,13} It has been suggested that lymphangiogenesis in MCC likely is driven by vascular endothelial growth factor- $C^{+}CD68^{+}CD163^{+}$ M2 macrophages.¹⁴ Another survival mechanism specific to polyomaviruses is their ability to interfere with the p53 tumor suppressor pathway.⁸ Loss of p53 expression by tumor cell nuclei has been associated with poor prognosis.¹⁵

Immune Response

Immune response as a role in tumor progression can be primarily centered on the concept of persistent antigen expression as a means of immune down-regulation. Dunn et al¹⁶ suggested that cancer cells must interact through 3 consecutive phases with the host immune system (immunoediting hypothesis). In the elimination phase, the host immune system is able to recognize and destroy newly transformed cells through both the innate and adaptive immune systems. The second equilibrium phase allows the tumor to remain dormant and growth remains stagnant. Lastly, the tumor is allowed to evade the immune system through the escape phase.⁸

Host immune responses play an important role in both the progression and prognosis of MCC. High anti-MCPyV capsid antibody titers have been associated with better progression-free survival in some patients.⁸ Patients with high antibody titers ($>10,000$) likely have better progression-free survival than those with low antibody titers ($<10,000$).¹⁷ Antibody titers to the LT antigen may serve as a biomarker of MCC disease burden in the future. Rising LT antigen titers have been shown to correlate with disease progression and falling titers correlate with successful treatment.⁸ Tumoral infiltration of $CD8^{+}$ T lymphocytes has been shown to be a predictor of survival compared to no intratumoral infiltration.⁶ Sihto et al¹⁸ suggested that this better prognosis from high intratumoral infiltration is not specific to MCPyV-positive MCC; however, it does highlight an important aspect of tumor evasion through the downregulation of cell surface expression of class I major histocompatibility complex antigens, which allows presentation of tumor intracellular peptides to $CD8^{+}$ T lymphocytes.⁸ Upregulation of this specific immune response may play a role in the future treatment of MCC.

Staging and Prognosis

Due to the extremely aggressive nature of MCC, patients with local disease and tumors 2 cm

or smaller in diameter have a 66% survival at 5 years.^{1,3} The 5-year survival rate for patients with local metastasis to regional lymph nodes ranges from 26% to 42%. Patients with distant metastasis have an 18% survival rate at 5 years.^{1,3} Data suggest that sentinel lymph node biopsy should be performed on all patients with MCC regardless of tumor size.¹ There are no consensus guidelines to date regarding imaging for the staging of MCC patients. It is suggested that (18F)fluorodeoxyglucose positron emission tomography alone or in combination with computed tomography (CT) may be of value as a single whole-body diagnostic tool for accurate staging.¹⁰ It also has been suggested that (18F)fluorodeoxyglucose positron emission tomography and CT may offer more accurate staging than other screening modalities such as CT alone or magnetic resonance imaging.^{14,19}

Treatment of MCC

Surgery remains the mainstay of treatment of MCC. Current National Comprehensive Cancer Network guidelines²⁰ recommend 1- to 2-cm margins for wide local excision or treatment with Mohs micrographic surgery. Sentinel lymph node biopsy should be performed intraoperatively in patients undergoing wide local excision and preoperatively for patients undergoing Mohs micrographic surgery due to potential alterations in lymphatic drainage that may affect lymphoscintigraphy.¹

Radiation may be used as primary or adjuvant therapy in patients with MCC. Radiation as primary therapy generally is reserved for patients who are not surgical candidates. It has been suggested that there was no difference in outcome in a small group of patients treated with radiation alone compared to patients who underwent surgery and radiation to the tumor bed.¹ Current guidelines suggest a small group of patients may not require adjuvant therapy following adequate resection of some small tumors, and clinical observation may be appropriate.^{1,3} Chemotherapy may play a palliative role in patients with metastatic MCC. Merkel cell carcinoma has been shown to be chemosensitive but with a high recurrence rate.¹ Because the immune system plays an important role in disease prognosis, having an intact immune system likely is paramount in the prevention of further disease progression.

Future Treatments of MCC

Future treatment of MCC may be focused on the viral etiology of most tumors and upregulation of the immune response, which may lead to the possibility of specifically interfering with virus-specific oncoproteins and stimulation of immune responses

to virally infected tumor cells.⁸ The MCPyV large T antigen has been found to be overexpressed in some tumors and may serve as a specific target of therapy.^{10,21} Survivin, a key cell cycle protein encoded by LT antigen, may be an interesting target given its implication in other cancers.¹³ Other potential nonviral molecular target antigens include the oncoprotein HIP1 that interacts with c-KIT.⁸ Specific immunostimulatory cytokines that may be used to upregulate the immune response to tumoral cells may include IL-2, IL-12, IL-15, or IL-21. Therapeutic agents that may be studied in the future to target the immune exhaustion phenomenon associated with tumorigenesis include ipilimumab (cytotoxic T lymphocyte antigen 4 receptor-blocking agent) as well as programmed cell death 1 and programmed cell death 1 ligand 1 (PD-1/PD-L1).⁸ Neuroendocrine tumors including MCC tend to be highly vascular and express vascular endothelial growth factors and platelet-derived growth factors, which may be other potential therapeutic targets. It has been reported that approximately 95% of MCC patients have CD56⁺ tumors, and current clinical trials suggest a promising therapeutic response with the immunogen anti-CD56 monoclonal antibody.³

Conclusion

Merkel cell carcinoma is a rare aggressive neuroendocrine tumor that has been associated with a novel polyomavirus. Merkel cell carcinoma tends to affect elderly and immunocompromised patients as well as white individuals. Tumors are most often found in areas of high UV exposure and clinically on sun-exposed skin. Merkel cell polyomavirus is associated with approximately 80% of tumors, and tumorigenesis likely is caused by a number of sequential steps from viral integration into host DNA, mutagenic events, and specific immune responses. Currently there are no consensus guidelines for using imaging for staging of MCCs, but sentinel lymph node biopsy is recommended for all cases due to the aggressive nature of even smaller tumors. Surgery remains the mainstay of treatment, and radiation therapy may be used as a primary or adjuvant treatment. Chemotherapy usually is reserved for patients with metastatic disease purely for palliation. Future treatments of MCC likely will center on the viral etiology of MCC and upregulation of immune responses to virally infected tumor cells.

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