International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1200-1204 www.ijprajournal.com ISSN: 2456-4494

"Merkel Cell Carcinoma: Pathogenesis, Clinical Features, Mechanotransduction, and Emerging Therapeutic Perspectives"

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Date of Submission: 05-02-2025 Date of Acceptance: 15-02-2025

ABSTRACT

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin cancer with a high propensity for local recurrence and distant metastases. It arises from mechanoreceptor Merkel cells in the skin. MCC typically presents as a painless, rapidly growing, erythematous to violaceous nodule on sun-exposed areas of older adults or immunosuppressed individuals.

The pathogenesis involves a complex interplay between ultraviolet (UV) radiation exposure and the Merkel cell polyomavirus (MCPyV), which is detected in a significant proportion of cases. The prognosis of MCC is influenced by tumor size, lymph node involvement, and the presence of metastases.

Management strategies for MCC require a multidisciplinary approach, including surgical excision, sentinel lymph node biopsy, radiation therapy, and systemic immunotherapy with immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway. The lesion is found in sun-exposed areas and presents as a small, violet, raised nodule. Immunohistochemical features are typically sufficient for diagnosis.

MCC is most common in the white population, and risk factors include advanced age, UV exposure, male sex, immunosuppression (such as AIDS/HIV infection, hematological malignancies, or solid organ transplantation), and Merkel cell polyomavirus infection.

Merkel cell carcinoma originates from Merkel cells in the epidermis, which are specialized epithelial cells involved in sensory perception. Symptoms often include a rapidly growing, painless nodule or ulcer on sun-exposed areas, particularly the head and neck.

OBJECTIVES

1. To understand the epidemiology, pathogenesis, and clinical presentation of MCC.
2. To recognize the importance of early detection and diagnosis of MCC.
3. To identify the risk factors associated with MCC, including UV radiation.
4. To describe the clinical features and diagnostic criteria for MCC, including histopathological and immunohistochemical characteristics.
5. To discuss the role of surgery, radiotherapy, and immunotherapy in the treatment of MCC.
6. To diagnose MCC accurately using a combination of clinical and histopathological criteria.
7. To manage the side effects and complications of MCC treatment, including radiation therapy, surgery, and immunotherapy.
8. To develop an individualized treatment plan for patients with MCC, considering the stage, location, and extent of the disease, as well as the patient's overall health and preferences.

KEYWORDS: Merkel cell polyomavirus (MCPyV), biomarkers, neuroendocrine carcinoma, Merkel cell carcinoma, immunosuppression, immunotherapy, radiation therapy, surgical therapy, etiology and treatment, skin cancer, immunohistochemistry, skin neoplasm, rare disease.

Total Words: 2265

I. INTRODUCTION

Merkel cell carcinoma (MCC) is an uncommon and highly aggressive skin cancer. It was first described as a trabecular carcinoma in 1972 by Cyril Toker. The presence of neurosecretory granules was detected within the tumor cells, which were similar to normal Merkel cells. The risk for developing MCC is increased in immunocompromised patients, such as those with chronic lymphocytic leukemia or HIV/AIDS.

MCC typically presents as a rapidly growing, erythematous lesion in the dermal layer of the skin. Merkel cells are located in the basal layer

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of the epidermis in vertebrates. While they function as mechanoreceptors, their exact origin remains uncertain.

This malignancy is most commonly associated with risk factors such as excessive UV exposure, advanced age, fair skin, and immunosuppression. Infection with the Merkel cell polyomavirus is also implicated in the development of a significant proportion of MCC cases.

MCC has a high potential for metastasis to regional lymph nodes and distant organs, making early diagnosis and treatment critical. The prognosis varies depending on the stage at diagnosis, with early detection offering the best outcomes.

TYPES OF MERKEL CELL CARCINOMA

MCC falls under the broader category of skin cancers, which include:

1. **Basal Cell Carcinoma (BCC)** – The most common type of skin cancer, arising from basal cells in the epidermis. It appears as a small, shiny, pearly bump or pink-red patch that may bleed or scab. BCC grows slowly and rarely spreads.
2. **Squamous Cell Carcinoma (SCC)** – The second most common type, arising from squamous cells in the epidermis. SCC appears as a scaly red patch, thickened growth, or sore that doesn't heal. It is caused by long-term UV exposure and is diagnosed via skin biopsy.
3. **Melanoma** – The most dangerous type of skin cancer, developing from melanocytes (pigment-producing cells). It often begins as a dark spot with irregular borders, asymmetry, multiple colors, or a diameter larger than 6 mm. Melanoma spreads quickly to lymph nodes and distant organs.
4. **Sebaceous Gland Carcinoma (SGC)** – A rare and aggressive malignancy arising from sebaceous glands, which produce oil for the skin and hair. It most commonly occurs on the eyelid but can develop in other sebaceous gland-rich areas.

EPIDEMIOLOGY AND ETIOLOGY

Before 1972, MCC was referred to as an undifferentiated skin carcinoma, and its diagnosis was uncommon before the 1980s. MCC is significantly more common in white individuals than in Black patients.

DERMIS

MCC (Merkel cell carcinoma) primarily develops in the dermis, which is the key layer involved in this malignancy. Tumor cells are typically located in the dermis as a dense proliferation of small, round, blue cells. An invasive skin cancer penetrates beyond the epidermis into the dermis, growing into surrounding healthy tissue.

SUBCUTANEOUS TISSUE

As MCC progresses, it often invades the subcutaneous fat and deeper layers, contributing to its aggressive nature. A pimple-like bump on the upper eyelid is a common symptom, but tumors can form anywhere on the body. A dermatologist performs a skin biopsy to remove the growth and examine it under a microscope for cancer cells.

HYPODERMIS IN SKIN CANCER

The hypodermis is the bottom layer of the skin. It functions in energy storage, connects the dermis to muscles and bones, provides insulation, and protects the body from harm

Merkel Cell Carcinoma (MCC) Overview

The exact cell of origin for MCC remains unknown. MCC is more common in males, particularly those with fair skin. Globally, MCC is a rare cancer, with an incidence of approximately 0.6 cases per 100,000 people annually. Higher rates are observed in countries with predominantly fair-skinned populations.

Etiology of MCC:

1. Serological evidence and clonal integration
2. UV radiation-induced DNA damage – Chronic exposure to UV radiation can lead to mutations in DNA, particularly in non-viral cases.
3. Immunosuppression – MCC is more common in individuals with compromised immune systems, such as HIV/AIDS patients and organ transplant recipients on immunosuppressive therapy.
4. MCPyV and Immune Response – The immune system normally controls MCPyV infection, but immunosuppression allows unchecked viral activity, leading to MCC development.

Risk Factors

- **Immunosuppression:** HIV/AIDS, organ transplantation, chronic lymphocytic leukemia.

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- **UV Radiation:** Long-term exposure increases the risk of DNA mutations.
- **Age and Gender:** MCC is more common in older individuals, particularly males.
- **Merkel Cell Polyomavirus (MCPyV):** Present in most MCC cases, its role in oncogenesis is significant.

STAGES OF MCC

1. Stage 0: In situ tumor (cancer localized and has not spread).
2. Stage 1A: Tumor is confined to its origin, with no lymph node involvement.
3. Stage 1B: Tumor is smaller than 2 cm, with no lymph node involvement.
4. Stage 2A: Tumor larger than 2 cm, with no lymph node involvement.
5. Stage 2B: Tumor larger than 2 cm, with deeper tissue invasion.
6. Stage 2C: Tumor has invaded deeper tissues such as bone, muscle, and cartilage.
7. Stage 3A: Cancer has spread microscopically to the lymphatic system.
8. Stage 4: Cancer has metastasized to distant organs or tissues.

Clinical Features of Merkel Cell Carcinoma (MCC)

Merkel cell carcinoma is an aggressive malignant tumor due to its high local, regional, and distant recurrence rates, as well as its significant metastatic potential. The clinical presentation of MCC is non-specific, and although it can affect any region of the body, it most commonly involves sun-exposed and sun-damaged areas. Nearly 50% of tumors occur in the head and neck region, while approximately 40% develop on the extremities.

MCC typically presents as a non-tender, rapidly growing, painless, firm, intradermal nodule that appears red to violaceous. The tumor can reach a considerable size over a short period.

Merkel Cell Function and Histology

Merkel cells are specialized epithelial cells that transduce touch stimuli and release neurotransmitters to excite sensory neurons, which then generate an action potential

MCC cells display a mixed immunohistochemical profile, characteristic of both epithelial and neuroendocrine origins. The common ectodermal origin of neuroendocrine and epidermal cells may explain this mixed phenotype. Additionally, the extracellular matrix is essential for the proper function of PIEZO channels, which are involved in mechanotransduction..

Mechanotransduction and Its Potential Role in MCC:

1. Tumor Microenvironment and Mechanotransduction

Changes in the stiffness of the extracellular matrix (ECM) are involved in tumor progression and metastasis in various cancers. In MCC, alterations in the skin ECM may contribute to tumor growth and invasion.

Integrins, which are transmembrane proteins involved in cell adhesion, play a key role in mechanotransduction by linking the ECM to the cytoskeleton. Their activation can trigger downstream signaling cascades, such as the PI3K/AKT and MAPK pathways, which are critical for cell survival and growth, including in MCC.

2. Merkel Cells and Ion Channels

Merkel cells function as mechanoreceptors, and ion channels such as Piezo1 and Piezo2 are essential for their mechanotransduction.

3. Hippo Signaling Pathway and MCCThe Hippo signaling pathway is sensitive to mechanical cues, such as cell density and substrate stiffness. This pathway regulates the activity of proteins associated with cancer aggressiveness. Its potential role in MCC progression remains an area of active exploration.

II. CONCLUSION

Merkel cell carcinoma is a rare but aggressive neuroendocrine skin cancer that primarily affects older adults or immunocompromised individuals. It is associated with risk factors such as UV exposure, immunosuppression, and Merkel cell polyomavirus infection.

MCC often presents as a painless, rapidly growing red or purple nodule on sun-exposed areas. Due to its aggressive nature, early detection and a multidisciplinary approach to management are essential. Surgery, radiation therapy, and immunotherapy are key treatment modalities.

While immunotherapy with checkpoint inhibitors has revolutionized the treatment of advanced MCC, further research is needed to optimize long-term treatment strategies.

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