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REVISIÓN

Update on Merkel Cell Carcinoma: Epidemiology, Etiopathogenesis, Clinical Features, Diagnosis, and Staging☆

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Abstract Merkel cell carcinoma (MCC) is a rare, highly aggressive tumor, and local or regional disease recurrence is common, as is metastasis. MCC usually develops in sun-exposed skin in patients of advanced age. Its incidence has risen 4-fold in recent decades as the population has aged and immunohistochemical techniques have led to more diagnoses. The pathogenesis of MCC remains unclear but UV radiation, immunosuppression, and the presence of Merkel cell polyomavirus in the tumor genome seem to play key roles. This review seeks to update our understanding of the epidemiology, etiology, pathogenesis, and clinical features of MCC. We also review histologic and immunohistochemical features required for diagnosis. MCC staging is discussed, given its great importance in establishing a prognosis for these patients.

PALABRAS CLAVE
Carcinoma de células de Merkel;
Clínica;
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Poliomavirus;
Estadificación

Actualización en el carcinoma de células de Merkel: Epidemiología, etiopatogenia, clínica, diagnóstico y estadificación

Resumen El carcinoma de células de Merkel (CCM) es un tumor poco frecuente, con un curso evolutivo muy agresivo, que con frecuencia origina recidivas locorregionales y metástasis. Asienta predominantemente en zonas fotoexpuestas en pacientes ancianos. Su incidencia se ha cuadriplicado en las últimas décadas debido al envejecimiento de la población y a un mayor diagnóstico gracias al uso de técnicas inmunohistoquímicas. La patogénesis del CCM no está clara, pero la radiación ultravioleta, la inmunosupresión y la presencia del poliomavirus MCPyV en el genoma del tumor parecen desempeñar un papel fundamental en el desarrollo de esta neoplasia.

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El objetivo de este artículo es realizar una revisión actualizada sobre los diferentes aspectos de la epidemiología, la etiopatogenia y la clínica del CCM. A su vez, detallamos los aspectos histológicos e inmunohistoquímicos necesarios para su diagnóstico y revisamos la estadificación por su importante trascendencia en el pronóstico de estos pacientes.

Introduction

Merkel cell carcinoma (MCC), also known as primary cutaneous neuroendocrine carcinoma, is an rare skin tumor that affects patients of advanced age. MCC is highly aggressive, and local and regional spread and metastasis are very common. Because the incidence of MCC has risen and a virus has been implicated in its pathogenesis, interest has increased in recent years.

This review aims to update our understanding of the epidemiology, etiology, pathogenesis, and clinical features of MCC. We review the histologic and immunohistochemical findings that lead to diagnosis and discuss the current staging system of the American Joint Committee on Cancer.

History

The author of the first description of a MCC tumor, which appeared in 1972, was Toker,[1] who used the term trabecular carcinoma of the skin to suggest the possibility of an origin in glandular tissue. An ultrastructural study by Tang and Toker[2] that appeared 6 years later demonstrated the presence of electron-dense granules in the cytoplasm of tumor cells. They proposed a neuroendocrine origin similar to that of Merkel cells in the epidermis. In fact debate on the cellular origin of these tumors continues, accounting for the proliferation of nomenclature used over time: cutaneous APUdoma, primary small cell carcinoma of the skin, anaplastic carcinoma of the skin, endocrine carcinoma of the skin, Merkeloma, primary cutaneous neuroendocrine carcinoma, and MCC.[3–5] These terms reflect neuroendocrine cell differentiation, the cell morphology observed, and a histologic similarity to small cell lung cancer.

The term cutaneous neuroendocrine carcinoma is the one that perhaps best reflects the immunohistochemical and ultrastructural features of these tumors, but the most commonly used and universally accepted name in the literature is MCC.

Epidemiology

MCC is a rare but characteristically aggressive tumor whose mortality rate is twice that of melanoma.[6] Less than 1% of malignant skin tumors are MCCs,[7] but it is the third most frequent cause of death from skin cancer after melanoma and squamous cell carcinoma.[8]

The incidence of MCC in Spain is unknown at this time. However, it has risen 3-fold in recent decades in the United States, from 0.15 per 100 000 population in 1981 to 1.44 per 100 000 population in 2011.[9,10] The increase is attributable to greater awareness of the disease among dermatologists and pathologists; greater ease of diagnosis thanks to immunohistochemical techniques; and increased population risk due to UV light exposure, aging, and immunosuppression.[11]

MCC affects mainly white populations but also appears exceptionally in black persons. The prevalence is somewhat higher in men than women in some professions (1.4:1) but no differences between the sexes are seen in others.[7,12]

MCC is diagnosed more often in persons of advanced age, and the incidence peaks between the seventh and eighth decades of life.[13] The mean age at diagnosis is 75 years. Only 5% of patients are under the age of 50 years, when the tumor is usually associated with some form of immunosuppression.[12] Nonetheless, cases have been described even in children, the youngest being 7 years old.[14]

Etiopathogenesis and Populations at Risk

MCC affects light-skinned individuals (phototypes I-III) on sun-exposed parts of the body and is associated with other skin tumors. These associations point to an etiopathogenic role for UV light,[15,16] but MCC has also been seen in patients who have undergone radiation or psoralen-UV-A therapy, in individuals exposed to arsenic,[17] and in skin areas affected by erythema ab igne.[18] MCC patients also develop other skin tumors induced by UV radiation (e.g., basal cell or squamous cell carcinomas and melanoma) that may appear either before or after MCC. Patients with melanoma are at 3-fold higher risk of MCC than the general population.[19]

The frequency is higher in immunocompromised individuals,[12,20] especially after heart[21] or kidney[22] transplants; during immunosuppressant treatment with azathioprine, ciclosporin, cyclophosphamide, and mTOR (target of rapamycin) inhibitors[23]; and in persons living with human immunodeficiency virus (HIV) infection.[24] Therefore, immune compromise is a risk factor for MCC, which also develops at younger ages and follows a more aggressive course in this context. MCC appears about 10 years after a transplant on average, and the ratio of melanoma to MCC is 1:6 in transplanted patients and 1:65 in the general population.

Risk for MCC is 13-fold higher in HIV-infected individuals than in the general population. A study of 14 HIV-infected patients with MCC found that most were males and on average younger (49 years old) at diagnosis than patients with MCC and no HIV infection (70 years old).[25] Other differences between the behavior of MCC in HIV-infected and noninfected persons are that the tumor develops in unexposed areas in the presence of HIV (35% on the buttocks) and that