

Merkel cell carcinoma: Clinical and anatomopathological features, management, and survival in our center

Carcinoma de células de Merkel: características clínicas y anatomopatológicas, manejo terapéutico y supervivencia en nuestro centro

Mónica Francés-Monasterio^{1*}, Ángela García-Minarro², Ana B. Paredes-Pérez³, and Orlando García-Duque¹

¹Department of Plastic and Reconstructive Surgery; ²Dermatology Department; ³Department of Pathological Anatomy. Hospital Universitario de Gran Canaria Dr. Negrín, Las Palmas de Gran Canaria, Spain

Abstract

Objective: The objective of this study was to summarize the features of the merkel cell carcinoma (MCC) and to systematize its diagnosis and therapeutic management. **Method:** We performed a literature review in PubMed, obtaining a total of 3308 articles, selecting ten for its complete reading and 22 for the reading of the summary according to the content. **Results:** In none of our patients, the MCC was the first suspected diagnosis. The treatment consisted in surgical excision with tumor free margins and lymphadenectomy. We offered adjuvant RT, in which they rejected. They remain disease-free at the present time. **Conclusions:** MCC is a rare and aggressive disease which presents as a fast-growing solitary asymptomatic erythematous nodule in those areas of skin which is exposed to sunlight in elderly patients. The main risk factors include radiative ultraviolet, immunosuppression, and merkel cell polyomavirus. Surgery is the main locoregional treatment. Lymph node metastases in the course of the disease are one of the main prognostic factors. If there are no adenopathies, sentinel lymph node biopsy must be done; if there are adenopathies or a positive biopsy, lymphadenectomy is indicated. Radiotherapy is indicated in all stages of disease since it has shown to improve locoregional control. In distant metastatic disease, immunotherapy and participating in clinical trials are the first choice.

Keywords: Merkel cell carcinoma. Surgical management. Clinical features. Radiotherapy.

Resumen

Objetivo: Resumir las características del carcinoma de células de Merkel (CCM) y sistematizar su manejo diagnóstico-terapéutico. **Método:** Realizamos una búsqueda bibliográfica en PubMed y aparecieron 3,308 artículos, de los que seleccionamos 10 para lectura completa y 22 para lectura del resumen acorde con su contenido. **Resultados:** En ninguno de nuestros pacientes el CCM fue la primera sospecha diagnóstica. El tratamiento consistió en la extirpación quirúrgica con márgenes libres y linfadenectomía. Se les ofreció radioterapia adyuvante, que rechazaron. Se encuentran libres de enfermedad tras 1 año del tratamiento. **Conclusiones:** El CCM es una condición rara y agresiva que se presenta como un nódulo eritematoso de rápido crecimiento y asintomático en zonas fotoexpuestas de pacientes añosos. Los principales factores de riesgo son la exposición ultravioleta, la inmunosupresión y el poliomavirus asociado al carcinoma de Merkel (MCPyV, Merkel cell polyomavirus). La cirugía es el pilar fundamental del tratamiento locorregional. La afectación ganglionar en el transcurso de la enfermedad es uno de los principales factores pronósticos. Si no existen adenopatías reconocibles, debe realizarse biopsia selectiva de

Correspondence:

*Mónica Francés-Monasterio

Pavía, Bajo izquierda

C.P. 35010, Las Palmas de Gran Canaria, España

E-mail: m.francesmon90@outlook.com

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ganglio centinela; si existen adenopatías o la biopsia es positiva, está indicada la linfadenectomía. La radioterapia adyuvante está indicada en todos los estadios y ha demostrado un mejor control locorregional. En la enfermedad a distancia es de primera elección la inmunoterapia y participar en ensayos clínicos.

Palabras clave: Carcinoma de células de Merkel. Tratamiento quirúrgico. Características clínicas. Radioterapia.

Introduction

Merkel cell carcinoma (MCC) is a skin carcinoma with neuroendocrine differentiation that has an increasing incidence (estimated at 0.7/100,000 people/year). Its pathogenesis is related to MCC-associated polyomavirus (MCPyV) and to chronic exposure to ultraviolet radiation (UVR)¹. Clinically, it usually occurs as a single, fast-growing, and asymptomatic erythematous nodule in photo-exposed regions of elderly people with fair skin, often simulating benign lesions. It is characterized by high local recurrence and by the presence of lymph node metastases, which reduce 5-year survival to 35%, or to 14% if there are distant metastases²⁻⁴. Advances in the knowledge of the pathophysiology and molecular genetics of this disease have allowed expanding the therapeutic armamentarium; however, surgery remains first choice.

Methods

The purpose of this article is to carry out a literature review of works that have been published to date about MCC, its clinical and anatomopathological characteristics, and its therapeutic management based on cases diagnosed in our center in the period encompassed from January 2018 to January 2019 (n = 2), to deepen the knowledge on this rare condition and evaluate the diagnostic-therapeutic management that has been carried out. We conducted a literature search in PubMed with the keywords MCC and 3308 articles appeared, out of which we selected ten for complete reading and 22 for abstract reading according to their content and publication date.

Case 1

The first case is an 87-year-old asymptomatic male, with a history of active smoking, hypertension, dyslipidemia, intermittent claudication, and benign prostatic hypertrophy. He was referred from the dermatology outpatient department for presenting, in the left frontal region, a papule-tumor pink lesion of 1.7 cm in diameter of 3 months' evolution, with clinical suspicion of



Figure 1. Case 1: frontotemporal lesion and parotid adenopathy initial clinical presentation.

basal cell carcinoma versus angiokeratoma (Fig. 1). A biopsy was performed that yielded the result of MCC. On the following examination, a nodule was found on the ipsilateral pre-auricular region, and fine-needle puncture aspiration indicated possible intraparotid lymph node metastasis. The CT scan did not show other relevant findings, and stage IIIB (T1N-1bM0) was determined. Surgical margins resection and superficial parotidectomy were uneventfully performed, and thus, the patient was discharged. On anatomopathological analysis, a 0.6 × 0.4 cm lesion was identified, with infiltrative growth pattern, which reached the dermis and hypodermis, respecting the surgical resection margins. Tumor thickness, measured from the stratum granulosum to the point of maximum infiltration, was 4 mm. With regard to tumor-infiltrating lymphocytes, a diffuse peritumoral lymphocytic infiltrate was observed at the base. Cells had a round, vesicular nucleus with dense chromatin, multiple nucleoli, and sparse cytoplasm. Mitotic count was 5–6 mitosis/HPF, with a Ki67 cell proliferation index > 90%. As for immunohistochemical profile, it expressed CK20 (dot-like pattern), CAM5.2, enolase, synaptophysin, and neurofilaments and was negative for TTF1 (Fig. 2). Superficial parotidectomy showed metastases to an intraparotid lymph node with periganglionic

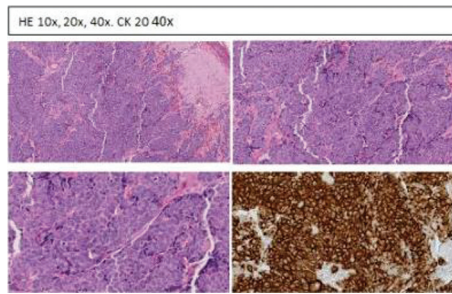


Figure 2. Case 1: left frontal region lesion histology.

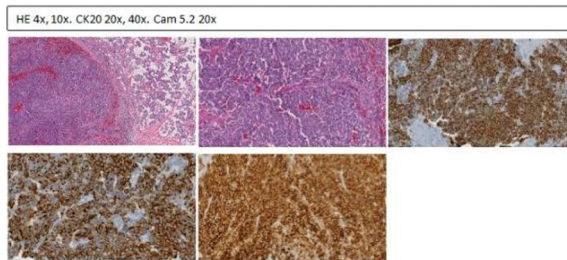


Figure 3. Case 1: lymph node metastasis.

tumor extension (Fig. 3). Twelve months after diagnosis, the patient has not experienced recurrence or disease progression.

Case 2

The second case is about a 78-year-old woman with a history of hypertension, poorly controlled type 2 diabetes mellitus, heart failure, and stable ischemic heart disease. She had a 6-month history of an asymptomatic smooth-surface erythematous tumor lesion on the back of the first toe of the right foot. Biopsy of the lesion showed clinical suspicion of lymphoma versus amelanotic melanoma (Fig. 4). In a second time, the right inguinal sentinel node resection and selective biopsy (SLNSB) was performed. Anatomopathological findings reported a 3.9-cm tumor with an infiltrative growth pattern, with vascular invasion and tumor extension to the surgical margin, consistent with MCC. Tumor thickness was at least 20 mm. Lymphocytic reaction was observed to be scarce and located throughout the invasive component of the tumor. The rest of histological and immunohistochemical features were similar to those described in the previous case. In addition, lymph node metastases without extranodal extension were identified in the inguinal sentinel node, with stage IIIA



Figure 4. Case 2: Initial lesion on the back of the right toe.

(pT4N1aM0) finally being established. After the case was presented to the Tumor Committee, surgical margins were resected, which were negative for residual disease; in addition, the right inguinal emptying was performed, which revealed subcapsular metastasis in one of the ten resected nodes (Fig. 5). The patient was discharged from the plastic and reconstructive surgery department at 3 months since she had no complications or residual disease and was referred to the dermatology outpatient department for follow-up, without recurrence of the disease being observed 18 months after diagnosis, with an Eastern Cooperative Oncology Group (ECOG) performance status of 4 (Fig. 6).

Adjuvant radiation therapy was offered to both patients, but they declined receiving it.

Discussion

MCC clinical diagnosis is a challenge due to its low frequency and clinical similarity with other lesions, which means that it is only considered as first diagnostic option in 1% of cases. The AEIOU acronym (Asymptomatic, rapid Expansion, Immunosuppression, Older than 50 years, and Ultraviolet exposure)⁵ has been proposed to assess it as a diagnostic possibility in those cases with more than three characteristics.

Genetic, molecular, and environmental factors interact in MCC pathogenesis. On one hand, UVR has been implicated, based on the higher incidence in geographical regions with higher levels of exposure and on its tendency to appear in photo-exposed areas (half occur on the head and neck)¹, and it is 25 times more common in fair skin and often adjacent to other lesions associated with UVR, with mutations of cytosine to thymine having been demonstrated (indicative of sunlight damage), especially in MCPyV-negative tumors^{1,6}.

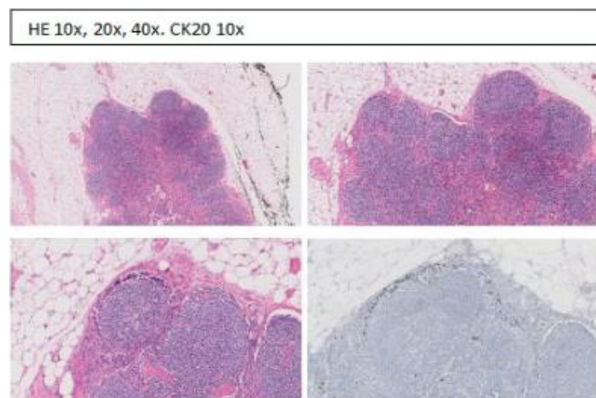


Figure 5. Case 2: the right inguinal metastasis histology.



Figure 6. Case 2: the right foot 3 months after surgery.

Between 60 and 97% of MCCs are MCPyV-positive, with this ubiquitous polyomavirus having been characterized for the first time in MCC tumor samples in 2008⁷, and its role in oncogenesis through clonal integration into the genome later being demonstrated⁶. In addition, immunosuppression increases the risk for the development of MCC, and immunosenescence could explain the increased incidence of MCC with age⁶.

Given the low incidence of this tumor and patients' advanced age, there is no established therapeutic algorithm, but it is accepted that, at Stages I-III, the treatment should be directed to the primary tumor and regional lymph node bed, with surgery with wide margins (1–3 cm) being of first choice⁸. The corresponding lymph node area should be explored in all patients, if possible with ultrasound. In case lymphadenopathies suspicious of malignancy are not found, SLNSB should be performed since, in up to one-third of these patients, microscopic lymph node disease will be substantiated⁹.

The presence of lymph node metastases is discovered in 30% of patients at diagnosis¹⁰ and in up to

80% during the course of the disease, with this being the main predictor of survival, together with clinical stage¹. If there are clinically palpable or radiologically suspicious lymphadenopathies, anatomopathological examination should be carried out. The treatment of lymph node metastases is lymphadenectomy. In these cases, an extension study is indicated.

Adjuvant radiotherapy to the tumor bed is indicated in all cases (especially if there are compromised margins, large tumors, clinically positive lymph nodes, and poor histological prognosis factors)⁹, given that MCC is highly radiosensitive. After lymphadenectomy, radiotherapy to the drainage territory may be considered. In cases, where it is negative, observation is recommended due to the low percentage of false negatives of this technique⁸. The notion that radiotherapy may decrease locoregional recurrence and improve overall survival is accepted, although to date, there are no randomized studies to demonstrate this. Radiotherapy as single treatment modality is used in patients who are not candidates for surgery⁹.

Factors of poor prognosis include compromised surgical margins (the most important with regard to local recurrence), age older than 70 years, male gender, size larger than 2 cm, location in the extremities and possibly immunosuppression states^{4,10}. On the other hand, MCPyV-positive tumors have a more favorable prognosis. Anti-MCPyV antibody titers are correlated with tumor burden and are modified in response to treatment, which is why monitoring recurrence with them has been proposed¹¹, although this determination is not available in our center. There are currently no other recognized immunohistochemical markers of poor prognosis.

As for patients with distant disease (stage IV), multidisciplinary management is required. First line of treatment is with immunotherapy, which includes PD-L1 (avelumab) and PD-1 inhibitors (pembrolizumab and nivolumab)¹⁰, which in non-randomized clinical trials have been observed to improve sustained response rates with regard to standard chemotherapy (cyclophosphamide, doxorubicin, vincristine, etoposide, and cisplatin), which can be an alternative in certain patients (immunotherapy contraindication, etc.). Inclusion in a clinical trial is preferable whenever possible¹⁰. Future therapeutic approaches include antiviral drugs, given the relationship with MCPyV.

Relapses occur within the first 3 years in 90% of cases, which is why the most recent guidelines¹⁰

recommend follow-up every 3-6 months for the first 3 years after diagnosis and subsequently every 6-12 months. The best test for the detection of metastases is positron-emission tomography; in order of frequency, metastases will affect the skin, lungs, liver, bones, brain, bone marrow, and other organs¹².

Conclusions

- MCC is a rare and aggressive condition that occurs as a fast-growing, asymptomatic erythematous nodule in photo-exposed skin areas of advanced-age patients.
- UVR, immunosuppression, and MCPyV are involved in its pathogenesis.
- Surgery is the cornerstone of MCC locoregional treatment.
- Eight out of every ten patients will exhibit lymph node involvement during the course of the disease, with metastasis being one of the main prognostic factors.
- If there are no clinically-radiologically recognizable adenopathies, SLNSB should be preferably carried out in the same surgical act; if there are adenopathies or SLNSB is positive, lymphadenectomy is indicated.
- Radiotherapy is accepted as an adjuvant at all stages and has shown better locoregional control.
- In distant disease, immunotherapy and participation in clinical trials are of first choice.

Conflicts of interest

The authors declare that they have no conflicts of interests.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments have been performed on humans or animals for this research.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

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